Studies toward the Total Synthesis of (+)-Pyrenolide D

Honors Research Thesis

Presented in partial fulfillment of the requirements for graduation

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by

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Abstract

Spiro lactones have had an extensive impact in both medicinal and organismal biology. Since their discovery, various methods for preparing spiro lactones have been studied and investigated. One of these spiro lactones, pyrenolide D, which is one of the four metabolites, A-D, was isolated from *Pyrenophora teres* by Nukina and Hirota in 1992 and shows cytotoxicity towards HL-60 cells at IC_{50} 4 μg/ mL. The structural determination, via spectroscopic methods, reported that unlike pyrenolides A-C, pyrenolide D contained a rare, highly oxygenated tricyclic spiro-γ-lactone structure and did not contain the macrocyclic lactone seen in the other pyrenolides. The purpose of this project is the determination of a cost effective and efficient synthesis of pyrenolide D from the naturally occurring sugar, D-xylose. Herein we report studies towards the total synthesis of pyrenolide D.

Acknowledgments

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Chapter 1: Introduction

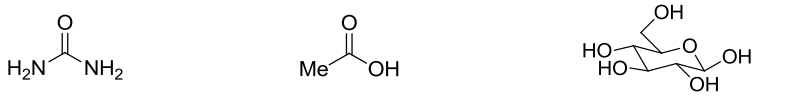
The contributions of organic synthesis throughout the last two centuries have brought us to the precipice of our understanding of and ability to design biologically and medicinally important compounds. Breakthroughs in chemistry, biology, biochemistry, and drug design have all been made possible by synthetic chemistry. The completion of total syntheses has produced molecules that improve our understanding of the world around us and save lives by curing illnesses.

Total synthesis can be used to synthesize natural products more efficiently, more cost-effective, and on larger scales than by simple isolation from their natural state.[1] Furthermore, by careful design of the synthetic route, these natural products can be altered from their original states to find more effective or more selective versions of these molecules. Through simple modifications, many natural products are able to be converted from being mildly potent to substances that are used every day to cure diseases and illnesses.

The design and complete documentation of a total synthesis is extremely difficult. Each atom must be constructed in a specific orientation and position throughout the entire reaction scheme. Reactions must be ordered in a way such that each piece of the molecule can be assembled without un-intentionally altering another portion of the same molecule. This can limit the types of reagents and reactions that may be employed through the total synthesis.

The modern synthetic era began in 1828 with the first total synthesis of urea (**1.1**) by Wohler.[2] Not only was this the first total synthesis ever documented, but it is also the first time an organic compound was made directly from an inorganic compound.[1] While urea is a

commonly and commercially available today, this landmark achievement marked the beginning of the use of total synthesis as a tool for the design of natural products, conformation of structure, and discovery of new biologically important molecules. The nineteenth century also afforded total syntheses of acetic acid (**1.2**) in 1845 by Kolbe[3] and glucose (**1.3**) in 1890 by Fischer.[4]



urea (Wohler, 1828)[1,2] 1.1

acetic acid (Kolbe, 1845)[1,3] 1.2

glucose (Fischer, 1890)[1,4] 1.3

Figure 1.1: Novel 19th century chemical syntheses

These pre-World War II era syntheses are characterized by the use starting materials that closely resemble the target molecules. This meant that very little innovation or analysis was required to synthesize these compounds. However, in the post-World War II era and with the rise of retrosynthetic analysis, syntheses became more complicated and desired molecules were constructed from simple, commercially available starting materials.

The post-World War II syntheses became more sophisticated as the result of five innovations:[5]

(1) Construction of detailed mechanisms for a host of organic reactions

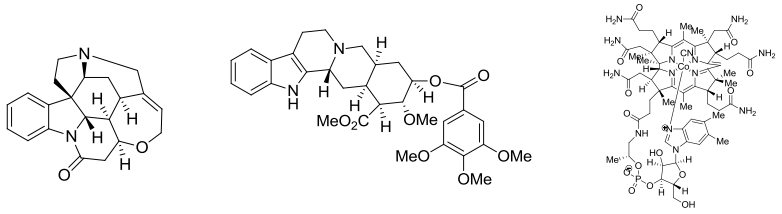
(2) Introduction of conformation analysis and stereo-chemical studies

(3) New spectroscopic tools for structural analysis

(4) Use of chromatography for analysis and separation

(5) Discovery of new selective chemical reagents

The next era is marked by the work of R. B. Woodward whose numerous total syntheses are marked by his use of rings to control stereo-chemical centers.[1] Woodward's most notable syntheses include strychnine in 1954,[6] reserpine in 1958,[7] and Vitamin B_{12} in 1973.[8] Woodward's contributions to synthetic chemistry in the design of natural products, are paramount to our understanding of modern chemical synthesis.

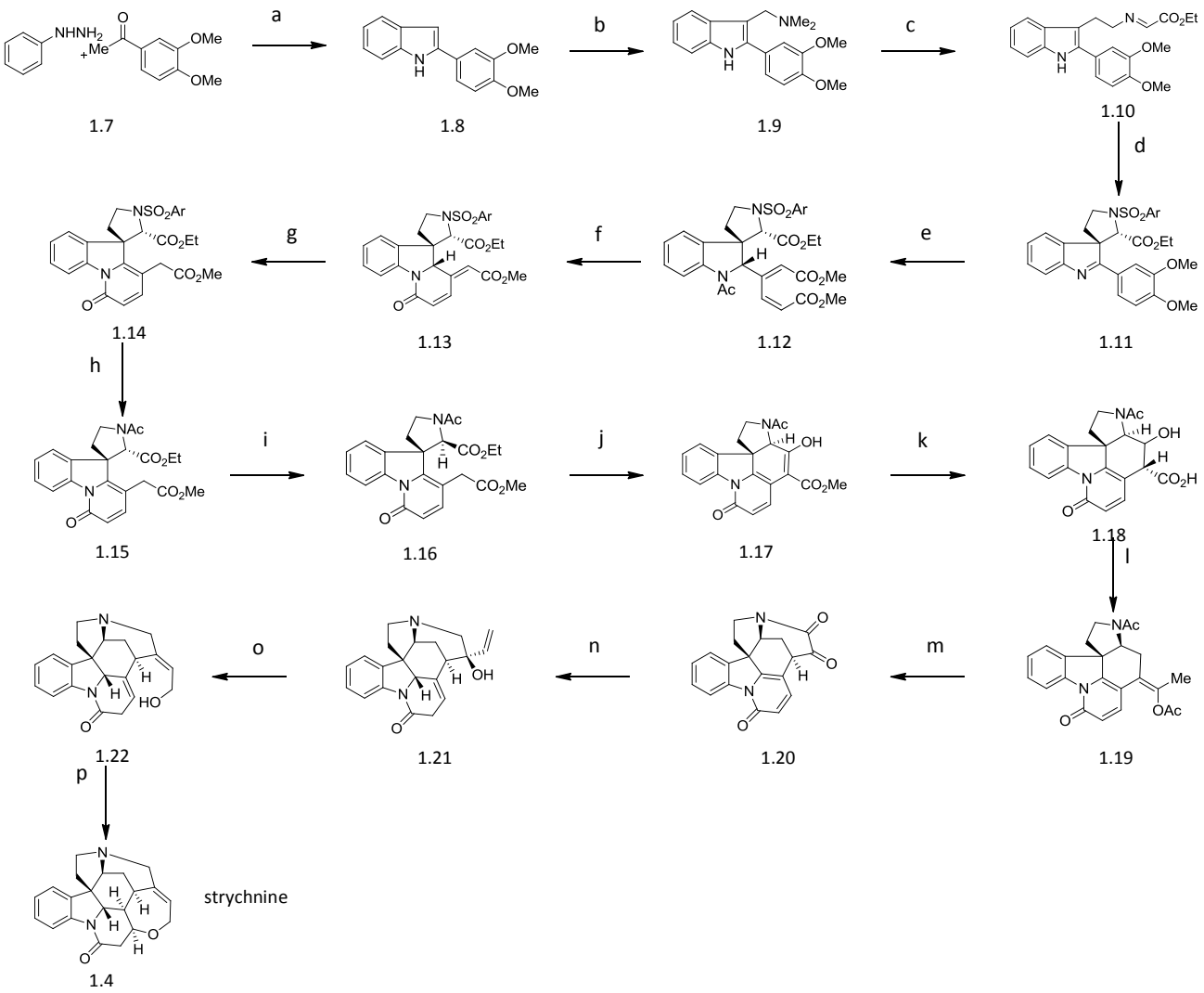


strychnine (1954) reserpine (1958) vitamin B_{12} (1973)

1.4 1.5 1.6

Figure 1.2: Selection of total syntheses by the Woodward group

Strychnine (**1.4**) was one of the first alkaloids to be naturally isolated and because of its unique structural features, its synthesis was highly coveted. In 1954, Woodward et al. completed the total synthesis of strychnine starting from acetoveratrone and phenylhydrazine.[6] The 28 step reaction scheme employed a Fischer indole synthesis using polyphospohric acid, a series of lactam formations to form the first and second rings, a Dieckmann condensation to form the third ring, and a conjugate addition to install the final ring. While elegant in design, Woodward's synthesis used the simplest of reagents to carry out even the most intricate reactions. Nicolaou said of Woodward's synthesis: "[it] ushered in a golden era of total synthesis and installed unprecedented confidence in, and respect for, the science of organic synthesis."[6]

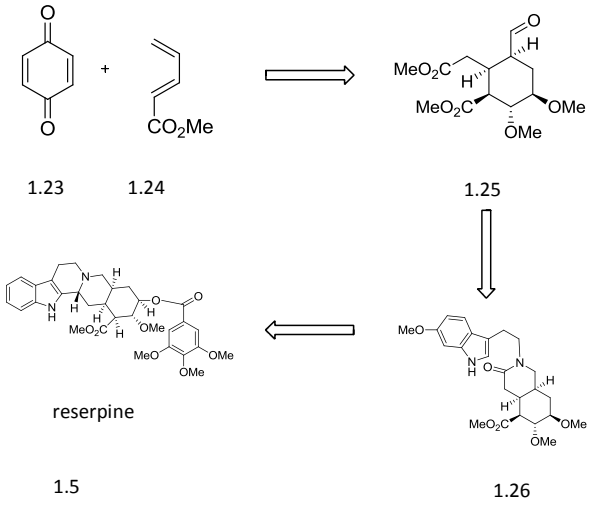


Scheme 1.1: Total synthesis of strychnine (1.4) (Woodward, 1954)[1,6]

(a) H_3PO4, (b) CH_2O, Me_2NH, AcOH, (c) i. MeI, ii. NaCN, iii. $LiAlH_4$, Δ, iv. EtOCOCHO, (d) p-TsCl, pyr, (e) i. $NaBH_4$, ii. Ac_2O, pyr, iii. O_3, AcOH, (f) MeOH, HCl, Δ, (g) isomerization, (h) i. HI, red phosphorous, ii. Ac_2O, iii. CH_2N_2, (i) NaOMe, MeOH, Δ, (j) dieckmann condensation (k) i. pTsCl, pyr, ii. $NaSCH_2Ph$, MeOH, iii. Raney Ni, Δ iv. H_2, Pd/C, v. KOH, H_2O, MeOH, (l) Ac_2O, pyr, (m) i. HCl, AcOH, ii. SeO_2, (n) i. ethynyl sodium, ii. H_2, Lindlar cat., iii. $LiAlH_4$, (o) i. HBr, AcOH, Δ, ii. H_2SO_4, Δ, (p) KOH EtOH

Four years later in 1958 Woodward's group completed the total synthesis of another alkaloid, reserpine (**1.5**), starting from the commercially available benzoquinone and (E)-methyl penta-2,4-dienoate.[7] First isolated in 1952,[9] reserpine (**1.5**) was soon found to have important medicinal properties, most notably its ability to treat hypertension as well as nervous and

mental disorders.[10] Woodward's synthesis of reserpine (**1.5**) demonstrated the ability to control stereochemistry by using unique ring properties.[1]

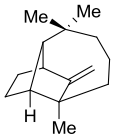


Scheme 1.2: Retrosynthesis of reserpine (1.5) (Woodward, 1958)[1,7]

Woodward's most important contribution to synthetic chemistry came in 1973 with the total synthesis of Vitamin B_{12}.[8] This novel synthesis gave organic chemists some of the most synthetically useful reactions including many new methods to form carbon-carbon bonds.

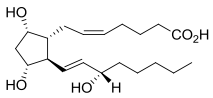
The next era in total synthesis is marked by E.J. Corey and his use of retrosynthetic analysis to design synthetic routes. Corey describes retrosynthetic analysis as a "problem-solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis."[2] The use of retrosynthetic analysis has forever changed how chemists approach total synthesis and has allowed the construction of many important natural products from cheap, simple starting materials. Some

of the Corey group's most notable syntheses include longifolene (**1.27**) in 1961[11] and Prostaglandin $F_{2\alpha}$ (**1.28**) in 1969.[12]



longifolene (1961)

1.27



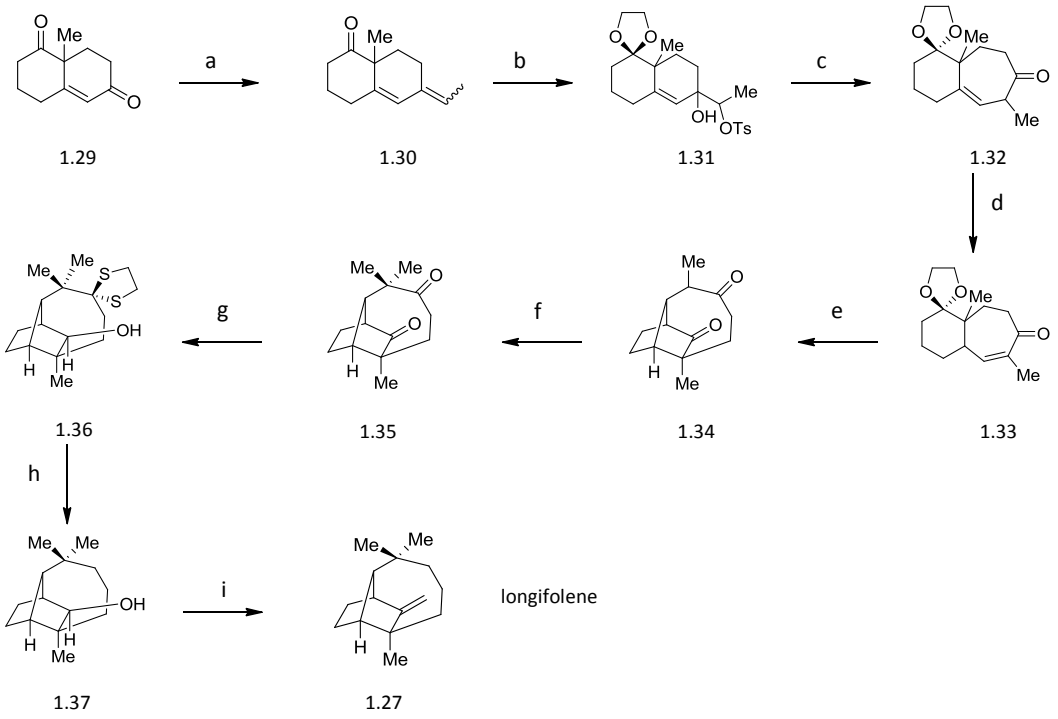
prostaglandin$F_{2\alpha}$ (1954)

1.28

Figure 1.3: Selection of total syntheses by the Corey group.

The power of retrosynthetic analysis was first put on display with Corey's synthesis of longifolene in 1961.[11] Analysis of this complex double bridge molecule gave way to cleavage at four possible carbon-carbon bonds. Through investigation of possible reactions to form the desired bonds which includes a Michael addition, internal S_N2 reaction, and cation-olefin addition, three possible precursors were formulated.[2] Analysis of these precursors showed the Michael addition precursor to be the most synthetically transparent as it could be easily prepared from a Wieland-Miescher ketone. This total synthesis, while trivial in nature, demonstrates the power of retrosynthetic analysis and the ability to synthesize complex molecules from simple starting materials.[2]

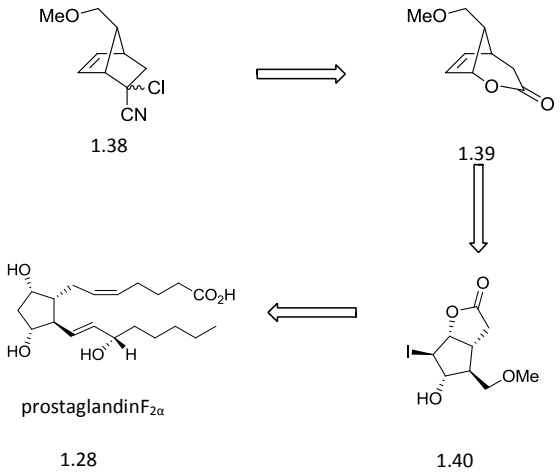
Corey's next important contribution occurred in 1969 with the total synthesis of prostaglandin $F_{2\alpha}$.[12] This compound, discovered in the 1930s[13] and determined structurally in the 1960s,[14] has important biological and potentially important medicinal properties. This synthesis outlines the synthetic importance of the Diels-Alder reaction and the versatility it provided as an intermediate.



Scheme 1.3: Total synthesis of longifolene (**1.27**) (Woodward, 1954)[1,6]

(a) i. $HO(CH_2)_2OH$, p-TsOH, Δ, ii. $Ph_3P{=}CHMe$, (b) i. OsO_4, pyr, ii. P-TsCl, pyr, (c) $LiClO_4$, $CaCO_3$, (d) 2N HCl, Δ, (e) $HO(CH_2)_2OH$, Et_3N, Δ, (f)Ph_3CNa, MeI, (g) i. $HS(CH_2)_2SH$, $BF\text{-}Et_2O$, ii. $LiAlH_4$, Δ, (h) i. Na, NH_2NH_2, Δ, ii. CrO_3, AcOH, (i) i. MeLi, Δ, ii. $SOCl_2$, pyr

The methods employed in Corey's synthesis of prostaglandins $F_{2\alpha}$ have been applied to a number of other prostaglandin analogs and have led to the synthesis of many other molecules.



Scheme1.4: Retrosynthesis of prostaglandin $F_{2\alpha}$ (**1.28**) (Corey, 1969)[1,12]

With the groundwork laid by Corey, Woodward, and others, total synthesis has taken off and become more important than ever in the scientific community. With the potential for many natural products to have biological properties, total synthesis has expanded and numerous reports are still being published detailing total syntheses of important natural products.

In 1980 Nukina, Ikeda, and Sassa first reported the structures of 10-membered keto lactones, pyrenolides A (**1.41**), B (**1.42**), and C (**1.43**), isolated from the fungus Pyrenophora teres.[15] The pyrenolides were isolated through the ethyl acetate extract of the fungus. The fungus was grown in a malt-dextrose solution for 1 month. The solution was then filtered through a XAD-2 column with methanol. The resulting solution was concentrated and purified via column chromatography (15:85 EtOAc: n-hexanes).[18] Spurred by the discovery that these metabolites possessed unique antifungal and growth inhibiting characteristics, these molecules were studied further and syntheses were proposed.

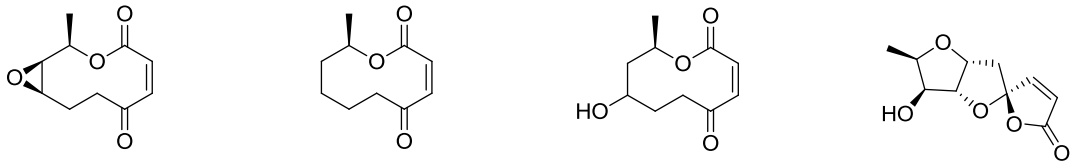
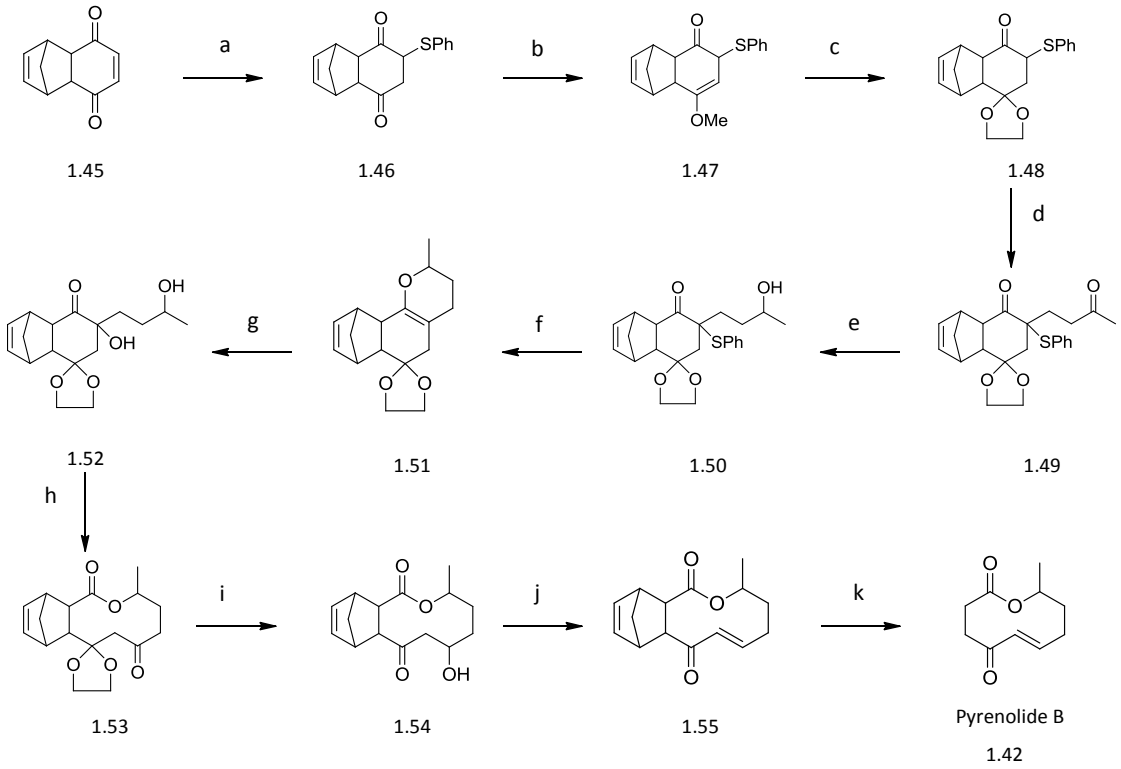


Figure 1.4: Structures of pyrenolides A-D.[17]

The first total synthesis of pyrenolide B (**1.42**) was proposed in 1985 by Asaoka, Naito, and Takei.[16] Starting from *p*-quinone and cyclopentadiene, the initial precursor was created through a Diels-Alder reaction. After a Michael addition and acetal protection the third ring

was formed through a PPTS dehydration reaction. The 10-membered keto lactone was then synthesized with a two-step oxidation with *m*-CPBA and lead tetraacetate. Finally, after removal of the acetal protecting group, a retro Diels Alder reaction afforded Pyrenolide B (**1.42**).

The total synthesis of pyrenolide C (**1.43**) was then completed by Wasserman and Prowse in 1992.[17] The synthesis was completed by using the commercial available 6-methyl-5-heptene-2-ol and following a 14 step reaction sequence. The highlights of this scheme include the synthesis of an α,β-unsaturated macrolide which was then converted to the trans epoxide

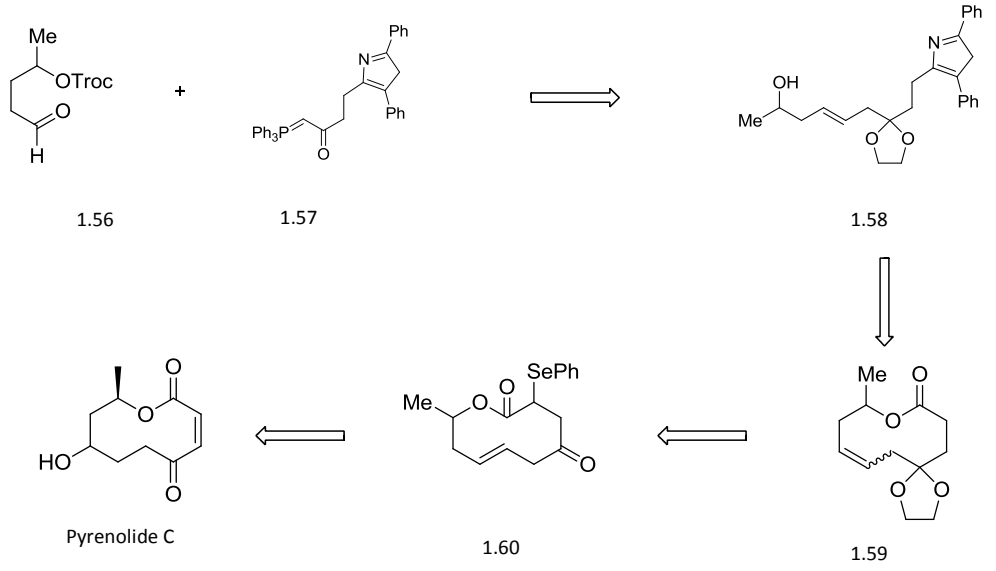


Scheme 1.5: Total synthesis of pyrenolide B (Asaoka, Naito, Takei, 1985)[16]

(a) PhSH, Et_3N, (b) MeOH, $HC(OMe)_3$, *p*-PTS, (c) $(CH_2OH)_2$, TMSCl, (d) MVK, *t*-BuOK, (e) i. $NaBH_4$, THF, MeOH, ii. Na-Hg, Na_2HPO_4, (f) PPTS, (g) *m*CPBA, Et_2O, H_2O, (h) i. $Pb(OAc)_4$, ii. $NaBH_4$, (i) PPTS, acetone, H_2O, (j) Et_3N, MsCl, (k) Δ

using *m*-CPBA. Finally, the epoxide was transformed into both diastereomers of pyrenolide C.

Later, in 1992, pyrenolide D (**1.44**) was isolate from Pyrenophora teres,[18] from which the other pyrenolides were originally isolated. It was hypothesized by Nukina and Hirota that pyrenolide D was formed through the hydration of the epoxide in pyrenolide A followed by a relactonization and subsequent acetal formation. These conditions were repeated in the laboratory, but all attempts to synthesize pyrenolide D in this manner were unsuccessful.

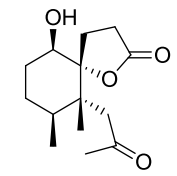


Scheme 1.6: Retrosynthesis pyrenolide C.[17]

Consequently, they hypothesized that this conversion occurred only through fungal metabolism. Structural studies showed that pyrenolide D possessed a unique highly oxygenated tricyclic spiro-γ-lactone structure. Further studies of pyrenolide D showed that while, unlike the other pyrenolides, it showed no activity towards fungi, it did show cytotoxicity towards HL-60 cells at IC_{50} 4 ug/mL.[18]

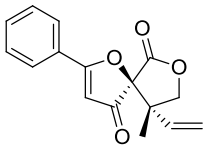
Recently, a number of isolated natural products have been found to possess this unique spiro-γ-lactone structure. This class of molecules has interesting biological activity and many

important pharmaceutical today rely on this structure. A few of the natural products that contain this unique structure are the antitumor agent allamandin,[19] the antiviral acylphloroglucinols,[20,21] Cephalosporolides H[22] and I,[23] and pathylactone A.[24] Some spiro-γ-lactones have also been used to construct units for binding protein kinase C.



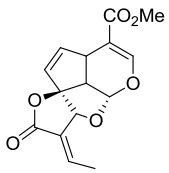
pathylactone A

1.61



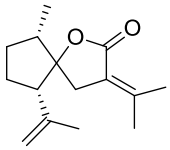
Hyperlactone C

1.62



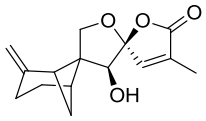
Plumericin

1.63



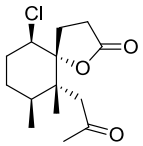
Curcumanolide A

1.64



Massarinoline A

1.65

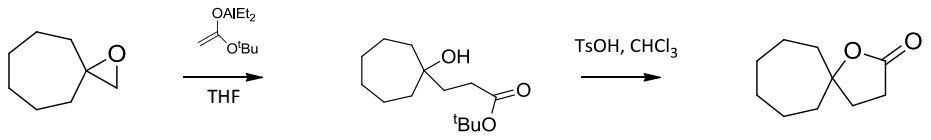


napalilactone

1.66

Figure 1.5: Selection of molecules that poses a spiro-γ-lactone.

As a result of the biological importance of the spiro-γ-lactone structure, many methods for its preparation have been proposed. One method proposed by Taylor et al. utilizes spiroepoxides which are opened with diethyl aluminum enolates to afford γ-hydroxy esters. These molecules were then closed with catalytic *p*-TsOH to yield the spiro-γ-lactone in yields from 45-76%.[25] Due to the potential for these molecules to have biological and medicinal uses, reports are still being published detailing syntheses of molecules containing this structure.



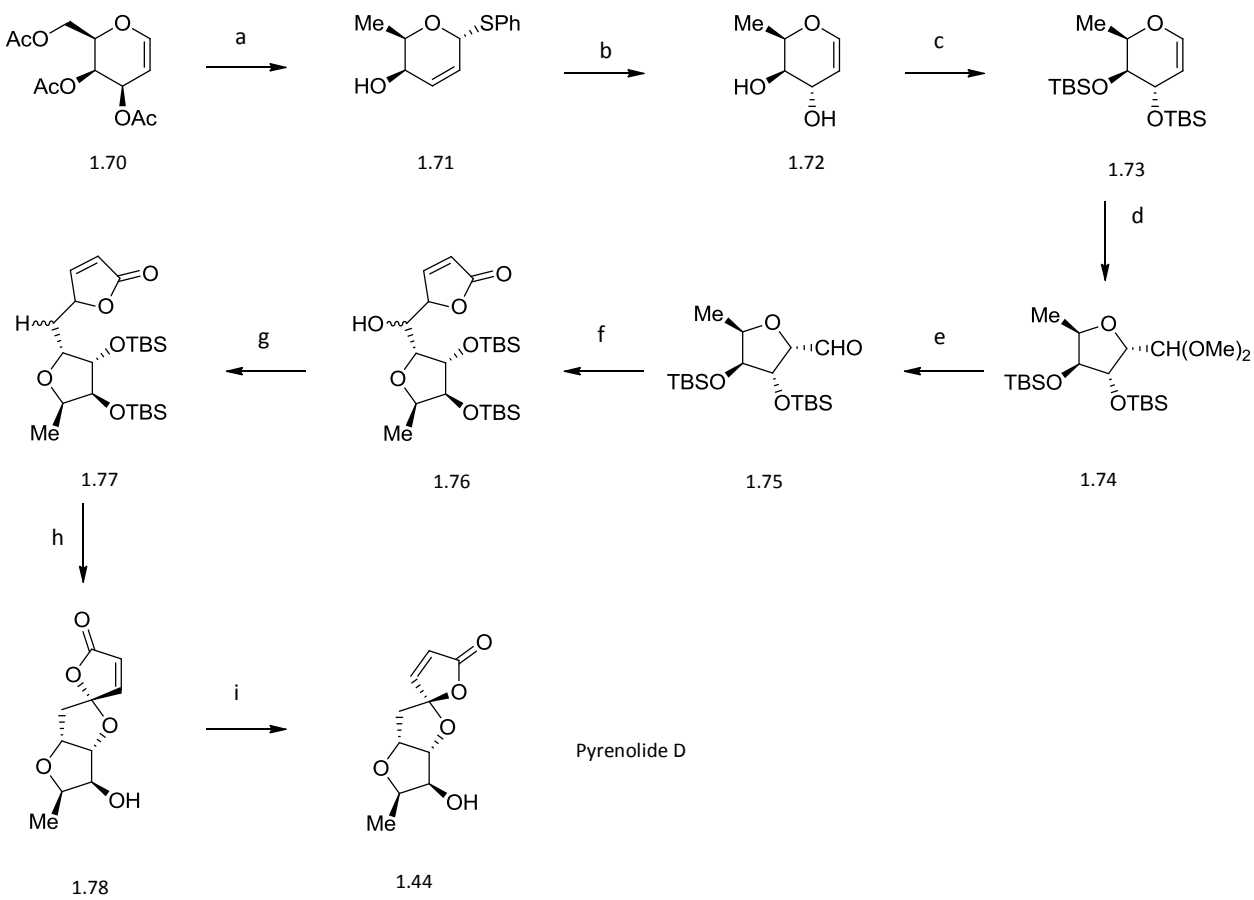
1.67 1.68 1.69

Scheme 1.7: Concise synthetic scheme of spiro-γ-lactone synthesis.[25]

The first total synthesis of pyrenolide D was completed in 2001 by David Gin.[26] Not only did they develop a short, concise synthetic route to the natural product, but the sequence also controlled for the absolute stereo-chemical configuration of pyrenolide D. The synthesis also developed a useful method for the construction of highly oxygenated tetrahydrofuran compounds from glycals.

Retrosynthetic analysis of pyrenolide D afforded disconnecting the molecule at the C_1 and C_2 positions and attaching together the highly oxygenated tertahydrofurfual derivative and 2-alkoxyfuran. While 2-alkoxyfuran is commercially available, a synthetic strategy to the tetrahydrofurfural compound needed to be established. Although there are multiple synthetic approaches to this compound, Gin used a stereoselective oxidative ring contraction of a glycol. By specifically using 6-deoxy-D-gulal (**1.75**), three of the four stereocenters in pyrenolide D were able to be established without need for stereospecific reactions or reagents.

Starting from the commercially available tri-*O*-acetyl-D-galactal (**1.70**), Gin employed a 5 step sequence including a Ferrier-type glycolsylation, acetate hydrolysis, selective tosylation, and oxidation reaction to the necessary intermediate. Finally, *tert*-butyldimethylsilyl (TBS) protecting groups were installed at C_2 and C_3 on the diol compound to afford the necessary precursor for the oxidative ring contraction reaction in an overall yield of 38%.



Scheme 1.8: Total synthesis of pyrenolide D (1.44) (Gin, 2001)[26]

(a) i. PhSH, $SnCl_4$, CH_2Cl_2, ii. NaOMe, MeOH, iii. Bu_2SnO, MeOH, iv. pTsCl, Bu_4NBr, $CHCl_3$, v. $LiAlH_4$, THF, (b) i. mCPBA, CH_2Cl, ii. Et_2NH, THF (c) TBS trifluoromethane sulfonate, 2,4,6-(tri-tert-butylpyridine), DMF, (d) PhI=O, Tf_2O, MeOH, CH_2Cl_2, (e) $TiCl_4$ Et_2O, (f) 2-(trimethylsilyloxy)furan, BF_3OEt_2, CH_2Cl_2, (g) Burgess reagent, PhF, (h) i. 1N LiOH, ii. HF, (i) 8N HCl, THF

Through the use of hypervalent iodine reagents, specifically iodosylbenzene in the presence of trifluoromethane sulfornic anhydride (Tf_2O), the oxidative ring contraction was achieved in a 5:1 ratio of the desired α-epimer. (**1.74**) This acetal compound (**1.74**) was converted to the corresponding aldehyde (**1.75**) through titanium tetrachloride ($TiCl_4$) deprotection (88%), while keeping intact all protecting groups. The commercially available 2-

(trimethylsilyl-oxy)furan was then added to the aldehyde with BF_3OEt_2 to construct the second ring.

The lactone (**1.76**) was dehydrated with the Burgess reagent and the third ring was constructed to give pyrenolide D (**1.44**) and its epimer (**1.78**) through lactone hydrolysis, de-protection of TBS groups, and spiroketalization. While this final reaction scheme gave a 50:50 mixture of pyrenolide D (**1.44**) and its epimer (**1.78**), Gin reported trivial separation of the epimers by chromatography. Consequently, the undesirable epimer can be re-equilibrated to give relatively high yields of pyrenolide D.

Not only did Gin's 2001 report give a complete synthesis of pyrenolide D with absolute stereochemistry of the natural product, but it also gave a novel way to perform oxidative ring contractions. This technique can be applied to other natural product syntheses.

In this thesis we propose a highly efficient and versatile synthesis of pyrenolide D starting from the natural sugar D-xylose. Our goal is two-fold. We hope to develop a cost-effective and concise total synthesis of pyrenolide D as well as demonstrate a new multipurpose spiro-γ-lactone formation that can be employed in other natural product syntheses. This new synthesis accomplishes the same goal as Gin's synthesis in 2001, while doing so in a cheaper and easier reaction scheme. Herein we describe the methods, advantages, and spectral determination of this new total synthesis of pyrenolide D.

References

(1) K. C. Micolaou, D. Vourloumis, N. Winssinger, P. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122.

(2) F. Wohler, *Ann. Phys. Chem.* **1828**, *12*, 145.

(3) H. Kolbe, *Ann Chem. Pharm.* **1845**, *54*, 145.

(4) E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890,** *23*, 799-805.

(5) E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis,* Wiley, New York, **1989.**

(6) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H.U. Daeniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, *76*, 4749-4751.

(7) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc.* **1956**, *78*, 2023-2055.

(8) R. B. Woodward, *Pure Appl. Chem.* **1968**, *17*, 519-547.

(9) C. F. Huebner, H. B. MacPhillamy, E. Schlittler, A. F. St. Andre, *Experientia*, **1955**, *11*, 303.

(10) A. Scriabine in *Pharmacology of Antihypertensive Drugs* (E.: A. Scriabine), Raven, New York, **1980**, 119.

(11) E. J. Corey, M. hno, P. A. Vatakencherry, R. B. Mitra, *J. Am. Chem. Soc.* **1961**, *83*, 1251-1253.

(12) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **1969**, *91*, 5675-5677.

(13) J.S. Bindra, R. Bindra, *Prostaglandin Synthesis*, Academic Press, New York, **1977**, 7.

(14) P.W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533-1563.

(15) M. Nukina, T. Sassa, M. Ikeda, *Tetrahedron Lett.* **1980**, *21*, 301-302.

(16) M. Asaoka, S. Naito, H. Takei, *Tetrahedron Lett.* **1985**, *26*, 2103-2106.

(17) H. Wasserman, K. S. Prowse, *Tetrahedron Lett.* **1992**, *33*, 5423-5426.

(18) M. Nukina, H. Hirota, *Biosci. Biotech. Biochem.,* **1992**, *56*, 1158-1159.

(19) S. M. Kupchan, A. L. Dessertine, B. T. Blaylock, R. F. Bryan, *J. Org. Chem.* **1974**, *39*, 2477.

(20) M. Tada, T. Takakuwa, M. Nagai, T. Yoshii, *Agric. Biol. Chem.* **1990**, *54*, 3061.

(21) K. Chiba, T. Takakuuwa, M. Tada, T. Yoshii, *Biosci. Biotech. Biochem.* **1992**, *56,* 1769.

(22) M. J. Ackland, J. R. Hanson, P. B. Hitchcock, A. H. Ratcliffe, *J. Chem. Soc.* **1985**, *1*, 843-847.

(23) J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Princep, *Nat. Prod. Rep.* **2005**, *22*, 15-61.

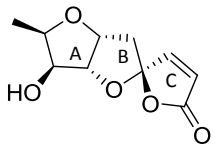
(24) J. –Y. Su, Y. –L. Zhong, L. –M. J. Zeng, *J. Nat. Prod.* **1993**, *56*, 288.

(25) S. Taylor, N. Chmiel, E. Mann, M. Silver, J. Vyvyan, *Synthesis* **1998**, 1009-1014.

(26) K. M. Engstrom, M. R. MEndoz, M. Navarro-Villablobs, D. Gin, *Angew. Chem. Int. Ed.* **2001**, *40*, 1128- 1130.

Chapter 2: Synthetic Studies and Experimental Data

Through retrosynthetic analysis we have devised a concise synthetic plan to pyrenolide D (**2.1**) starting from D-xylose. (**2.2**) The main benefit of using D-xylose is that 3 of the 4 stereo-centers of the initial ring can be obtained from the starting material. This will greatly simplify the synthesis and the number of steps required to isolate pyrenolide D stereo-selectively. Furthermore, by starting from a sugar such as D-xylose, we can easily make small alterations to the synthetic route, starting from another aldose and create diastereomers of pyrenolide D. This can possibly lead us to a more biologically active derivative of the natural product.

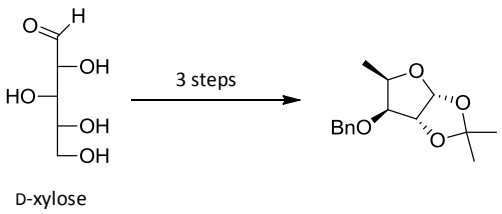


2.1

Figure 2.1: Structure of Pyrenolide D with definition of rings.

We have separated the total synthesis of Pyrenolide D into three separate schemes, each representing the formation and configuration of one of the three rings (A, B, C). Throughout the paper, positions on the initial ring will be referred to as C_n where n is between 1 and 5. These positions will correspond to the carbons in the ring in a clock wise fashion starting from the ring oxygen. Scheme 2.1 includes the preparation of the initial ring A and installation of the necessary protecting groups.

The first reaction converts D-xylose (**2.2**) into its furanose form and installs the acetal protecting group across C_1 and C_2. The protecting group is also added at this point so the

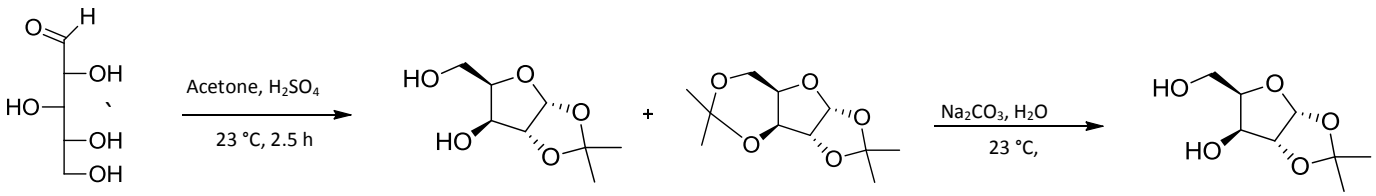


2.2 2.3

Scheme 2.1: Construction of ring A in pyrenolide D

substituents at C_3 and C_4 can be altered as need without affecting C_1 and C_2. As seen in scheme **2.2**, the reaction will produce a mixture of the mono (**2.4**) and diacetonide (**2.5**). Solid D-xylose was dissolved in a mixture of acetone and catalytic sulfuric acid for approximately 30 min.[1] After this period, sodium carbonate dissolved in water was added slowly and the mixture was stirred for 2.5 hours. Solid sodium carbonate was added until the resulting mixture was basic and the reaction was filtered. This solution was concentrated under reduced pressure and purified via column chromatography (silica gel) to afford **2.4** in a 94% yield.

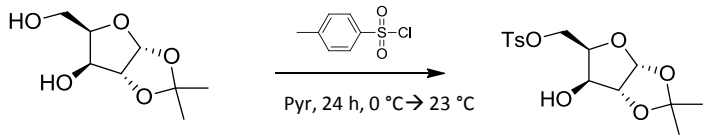
With compound **2.4** in hand, we attempted deoxygenation at the C_5 position to afford the deoxygenation found in pyrenolide D. We first converted the C_5 hydroxyl into a tosylate ester that can be reductively removed to give the 5-deoxy compound.



2.2 2.4 2.5 2.4

Scheme 2.2: Installation of acetal protecting group on D-xylose.

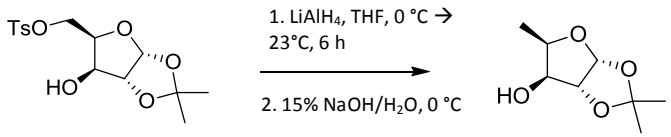
The hydroxyl group at C_5 was selectively tosylated with *p*-toluenesulfonyl chloride. Compound **2.4** was dissolved in pyridine and *p*-toluenesulfonyl chloride was added slowly at 0 °C.[2] The reaction was allowed to proceed for 24 hours with warming to room temperature after which the mixture was partitioned between dichloromethane and water. The resulting organic solution was concentrated under reduced pressure and purified via column chromatography (silica gel) to give **2.6** in a 63% yield.



2.4 2.6

Scheme 2.3: Tosylation of C_5 OH.

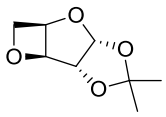
Compound **2.6** was reduced at the C_5 position using solid lithium aluminum hydride ($LiAlH_4$) in dry THF under a nitrogen atmosphere. The mixture was cooled to 0 °C and **2.4** dissolved in dry THF was added slowly over 30 minutes.[3] The reaction proceeded at room temperature for 6 hours and was quenched using the Fieser method.[4] The neutral solution was filtered and extracted with ethyl acetate and water. The resulting organic solution was concentrated under reduced pressure and purified via column chromatography (silica gel) to afford **2.7** in a 96% yield.



2.6 2.7

Scheme 2.4: $LiAlH_4$ reduction of tosylate group at C_5.

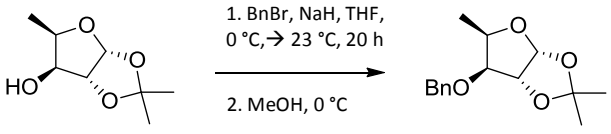
During the first attempts of this reaction, an alternate product was formed and confirmed thorough NMR analysis. This cyclized product (**2.8**) is thought to form when the mixture is not cooled sufficiently and the tosylated compound is added at or near ambient temperatures. Compound **2.8** forms when the hydroxyl group at C_3 is deprotonated and preforms and intramolecular substitution reaction. The formation of this molecule was avoided in later attempts with sufficient cooling during the addition of lithium aluminum hydride.



2.8

Figure 2.2: Side product from $LiAlH_4$ reduction reaction

To complete the synthesis of ring A, a benzyl protecting group was installed at the C_3 position. A protecting group is installed to prevent any alternate reactions from occurring throughout the remainder of the synthesis.

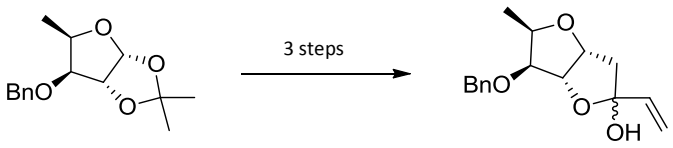


2.7 2.3

Scheme 2.5: Synthesis of benzyl ether at C_4.

Solid sodium hydride was dissolved in dry THF, cooled to 0 °C, and kept under a nitrogen atmosphere. **2.7** and benzyl bromide were dissolved in a mixture of THF, which was then added slowly over 50 minutes to the original solution.[5] After addition, the reaction vessel was

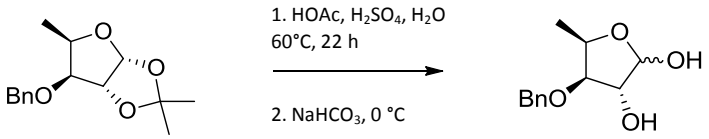
sealed and allowed to react for 20 hours at room temperature. Once the reaction was complete, the mixture was quenched with methanol and the solution was extracted with diethyl ether. This solution was concentrated under reduced pressure and purified via column chromatography (silica gel) to afford **2.3** in a 92% yield.



2.3 2.9

Scheme 2.6: Construction of ring B in pyrenolide D.

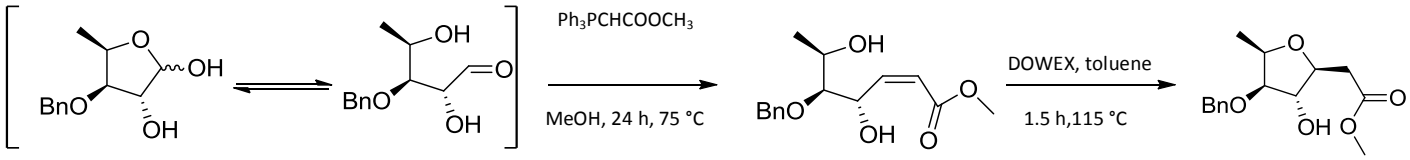
In scheme 2.6 the construction of ring B into the lactone is shown after removal of the acetal protection group across C_1 and C_2. In the first reaction, the acetal protecting group on **2.3** was removed through aqueous acid catalyzed hydrolysis. At 0 °C, water, acetic acid, sulfuric acid, and **2.3** were combined and stirred.[3] The mixture was then heated at 60 °C for 22 hours at which time the reaction was quenched with solid sodium bicarbonate. After concentration under reduced pressure, the compound was purified via column chromatography (silica gel) to afford **2.10** in a 54% yield. The anomeric acetal proved to be very robust a more efficient removal remains a point for improvement and future studies.



2.3 2.10

Scheme 2.7: Hydrolysis of acetal protecting group.

The second ring was established off of the C_1 and C_2 position through tandem Wittig olefination reaction followed by ether formation by addition to the β position of the resulting α,β unsaturated ester and subsequent lactonization. In the first attempts of the reaction, **2.10** was dissolved in methanol and methyl triphenylphosphine acetate was added at ambient temperature. The mixture was refluxed overnight at 75 °C and then concentrated under reduced pressure and isolated via column chromatography.



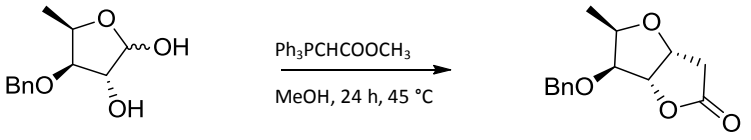
2.10 2.11 2.12 2.13

Scheme 2.8: Olefination studies

Through NMR spectroscopic analysis, we determined that compounds **2.13** and **2.14** were isolated as a mixture. We determined that the Wittig reaction yielded a mixture of the cis/trans olefins which led to ether formation resulting is diastereomeric furanal methyl esters. The resulting relationship between the hydroxyl group and the methyl ester allows for further lactonization. The trans ester product cannot lactonize due to distance between the substiutents at C_1 and C_2. In order to improve the reaction, we conducted studies, altering the solvent, concentration, and temperature to favor formation of the cis alkene that can successfully undergo the tandem events to form lactone **2.14**.

After several studies, we defined optimal conditions for the reaction using methanol at a

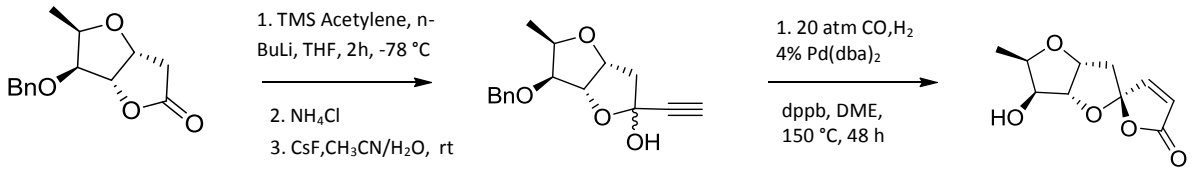
temperature of 45 °C for 24 hours.[6] Characterization of this compound proved that **2.14** was isolated in a 78% yield.



2.10 2.14

Scheme 2.9: Wittig olefination and lactonization reaction

We attempted to finish the synthesis through a 2 step reaction sequence that included a nucleophlic addition of ethynyltrimethylsilane to form the corresponding hemiacetal and then a unique reductive carbon monoxide insertion and lactonization to form the final ring. Unfortunately, all attempts at the initial nucleophilc addition were unsuccessful. NMR spectroscopic analysis of the crude reaction mixture yielded mostly unreacted starting material. Consequently, another synthetic route to pyrenolide D had to be established.



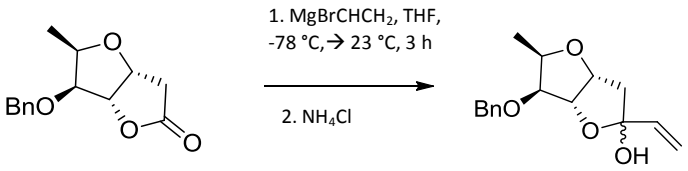
2.14 2.15 2.1

Scheme 2.10: Previous synthetic scheme to form ring C in pyrenolide D.[7,8]

The alternative synthesis was designed as a 3 step reaction sequence which would include a Gringard addition, esterification, and an olefin metathesis reaction. The Gringard

addition was used to install the vinyl group off the second ring and convert the carbonyl group to the corresponding hemi ketal.

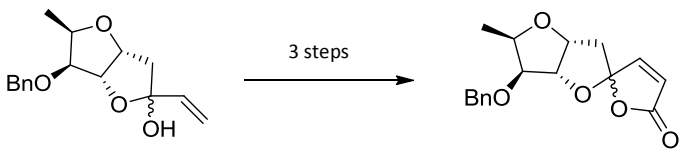
A mixture of dry THF and vinyl magnesium bromide was combined under a nitrogen environment, cooled to -78 °C, and allowed to stir for 20 minutes.[9] **2.14**, dissolved in dry THF was added slowly at -78 °C. The reaction proceeded for 3 hours and was quenched with sat. ammonia chloride. The product was concentrated under reduced pressure and purification via column chromatography (silica gel) afforded **2.9** (mixture of diastereomers) in a 64% yield. The product was confirmed through ^{1}H NMR and GCMS analysis.



2.14 2.9

Scheme 2.11: Grignard addition of vinyl magnesium bromide to lactone (B).

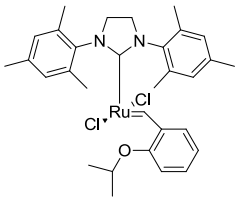
With compound **2.9** in hand, we envisioned construction of the final ring, which included de-protection to afford pyrenolide D. Should the final scheme yield the spiroketal epimer of pyrenolide D, we propose re-equilibration with 8N HCl, using a procedure similar to that in David Gin's synthesis, to maximize production of the thermodynamically more stable spirokietal, pyrenolide D.



2.9 2.17

Scheme 2.12: Construction of ring C in pyrenolide D.

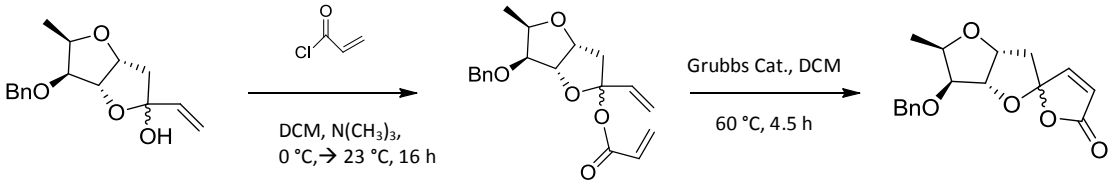
Scheme **2.12** begins with the hydroxyl group being converted into the α,β-unsaturated ester. **2.9** was dissolved in dry DCM and triethylamine, sealed, and placed under a nitrogen atmosphere. The solution was cooled to 0 °C and acryloyl chloride was added slowly.[10] The reaction proceeded at room temperature for 16 hours. After TLC analysis showed the reaction to be complete, the mixture was concentrated under reduced pressure and isolated via column chromatography (silica gel) to afford **2.16** in a 73% yield.



2.15

Figure 2.3: Structure of Grubbs Catalyst (2nd generation)

We next attempted cyclization via a ring closing olefin metathesis reaction. **2.16** was dissolved in dry DCM and Grubbs Catalyst (2nd generation) was added. The reaction was flushed with nitrogen, sealed, and headed at 40 °C for 4.5 hours.[11] GC/MS spectroscopic analysis showed a mixture of **2.16** and **2.17** was produced in a 2:3 ratio. In hopes of completing the synthesis, the crude product was confirmed only by mass spectrometry and used without purification in the subsequent deprotection step.

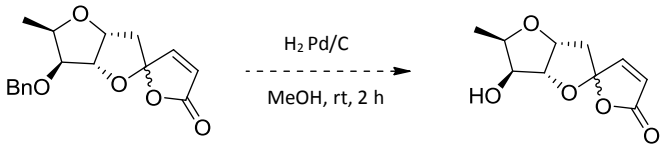


2.9 2.16 2.17

Scheme 2.13: Formation of ring C in pyrenolide D.

The final step in the reaction was to remove the benzyl protecting group at C_4 through a hydrogenation reaction. Unfortunately, all attempts to remove the benzyl group yielded recovered starting material and decomposition products.

In the future, we hope to synthesize pyrenolide D and derivatives using the methods outlined above. Should the benzyl protecting group on compound **2.17** prove to be impossible



2.17 2.18

Scheme 2.14: Deprotection of benzyl protecting group by hydrogenation

to remove, we propose the use of an alternate protecting group such as the *tert*-butyldiphenyl or PMB group. Furthermore, we hope to further optimize the procedure used to prepare compound **2.14**.

References

(1) J. Moravcova, J. Capkova, J. Stanek, *Carbohydrate Research*. **1994**, *263*, 61-66.

(2) J. Moravcova, J. Capkova, J. Stanek, I. Raich, *J. Carbohydrate Chemistry.* **1997**, *16*, 1061-1073.

(3) S. Chandrasekhar, B. Saritha, V. Jagadeshwar, S. J. Prakash, *Tetrahedron Lett*. **2006**, *17*, 1380-1386.

(4) L. Fieser, M. Fieser, *Reagents for Organic Synthesis* **1967**, 581-595.

(5) H. Takaku, K. Kamaike, *Chem. Lett.* **1982**, 189-192.

(6) H. B. Mereyala R. R. Gadikota, *Chem. Lett.* **1999**, 273.

(7) W. Pitsch, A. Russel, M. Zabel, B. Konig, *Tetrahedron Lett.* **2001**, *57*, 2345-2347.

(8) B. Ali, H. Alper, *J. Org. Chem*. **1991**, *56*, 5357-5360.

(9) N. Kishali, M. F. Polat, R. Altundas, Y. Kara, *Helvetica Chimica Acta*. **2008**, *91*, 67-72.

(10) S. Martwiset, O. Yavuzcetin, M. Thorn, C. Versek, M. Tuominen, E. B. Coughlin, *Journal of Polymer Science.* **2008**, *47,* 188-196.

(11) M. Fujii, M. Fukumura, Y. Hori, Y. Hirai, H. Akita, K. Nakamura, K. Toriizuka, Y. Ida, *Tetrahedron*. **2006**, *17*, 2292-2298.

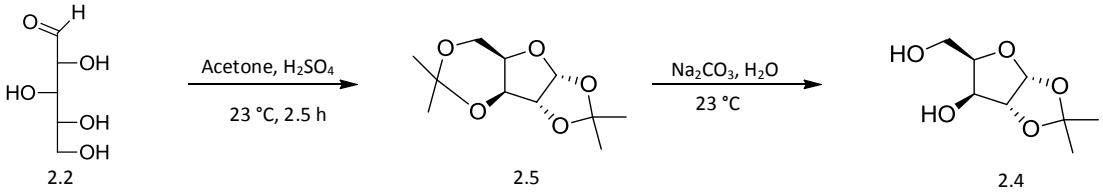
(12) K. M. Engstrom, M. R. MEndoz, M. Navarro-Villablobs, D. Gin, *Angew. Chem. Int. Ed.* **2001**, *40*, 1128- 1130.

Experimental

General:

Solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out under a positive pressure of nitrogen and were monitored by TLC on silica gel 60 F254 (0.25 mm, E. Merck). Spots were detected under UV light, PMA in ethanol, or *p*-anisaldehyde. Solvents were evaporated under reduced pressure and below 40 °C (bath). Organic solutions of crude products were dried over anhydrous $MgSO_4$. Chromatography was performed on silica gel 60 (40-60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Melting points are uncorrected. ^{1}H NMR spectra were recorded at 250 and 400 MHz, and chemical shifts are referenced to TMS (0.0, $CDCl_3$). ^{13}C NMR spectra were recorded at 100 MHz, and ^{13}C shifts are referenced to $CDCl_3$ (77.0, $CDCl_3$). Electrospray mass spectra were recorded on samples suspended in mixtures of DCM and/or $CDCl_3$.

Synthesis of **2.4**:

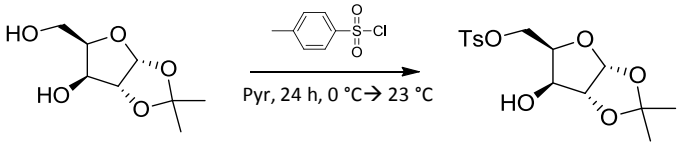


2.2 2.5 2.4

Synthesis of (3aR,5R,6S,6aR)-5-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**2.4**). To a 2.0 L RBF equipped with a magnetic stirbar was added acetone (650 mL) and H_2SO_4 (25 mL, 450 mmol). The solution was cooled in an ice bath (0 °C) and D-xylose (25.00 g, 166.5 mmol) was added slowly. The mixture was warmed to rt (23 °C) and stirred for 30 min. After this time, Na_2CO_3 (32.5 g) dissolved in water (280 mL) was added dropwise and the

mixture was reacted for 2.5 h. Solid Na_2CO_3 (40 g) was added until the solution was basic and the mixture was dried with Na_2SO_4. The solids were separated by vacuum filtration and the organic phase was concentrated under reduced pressure and purified by column chromatography as a yellowish oil (silica, 30:1 DCM:methanol) to give **2.4** (29.9 g, 157 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.44 (s, 3H), 3.68 (s, 1H), 3.89 (m, 2H), 4.13 (m, 1H), 4.23 (m, 1H), 4.47 (m, 1H), 4.79 (s, 1H), 5.91 (d, 1H, J = 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.30, 26.60, 60.23, 73.10, 75.49, 80.02, 85.33, 104.68, 111.75; HRMS [M+Na] calc= 213.0733, obs= 213.0729; R_f = 0.30 (3:1 petroleum ether:ethyl acetate) *The experimental data for this compound matched those previously reported in the literature.

Synthesis of **2.6**:

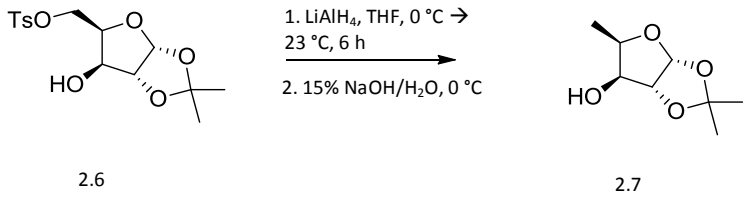


2.4 2.6

Synthesis of ((3aR,5R,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl 4-methylbenzenesulfonate (**2.6**). To a 2.0 L RBF equipped with a magnetic stirbar was added **2.4** (20.3 g, 107 mmol) and pyridine (82.4 mL). The solution was cooled in an ice bath (0 °C) and while stirring, solid *p*-toleuenesufonyl chloride (47.8 g, 250 mmol) was added. The mixture was stirred for 24 h and then partitioned between DCM and water (6 x 50 mL). The combined organic extracts were dried with Na_2SO_4, filtered and the organic phase was concentrated under reduced pressure. The crude oil was purified by column chromatography

(silica, 20:1 petroleum ether:ethyl acetate) to yield **2.6** as an off-white solid (23.2 g, 67.4 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 6H), 2.47 (m, 3H), 4.02 (m, 2H), 4.33 (m, 2H), 4.51 (m, 1H), 4.76 (m, 1H), 5.87 (m, 1H), 7.39 (m, 2H), 7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.74, 21.64, 26.20, 65.86, 81.23, 82.98, 85.52, 111.39, 112.77, 127.94, 130.19, 145.55; HRMS [M+Na] calc= 367.0822, obs= 367.0830; R_f = 0.64 (2:1 petroleum ether:ethyl acetate) *The experimental data for this compound matched those previously reported in the literature.

Synthesis of **2.7**:

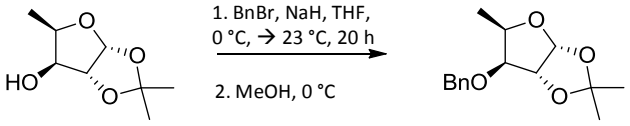


2.6 2.7

Synthesis of (3aR,5R,6S,6aR)-2,2,5-trimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**2.7**). To a flame dried 2.0 L RBF equipped with a magnetic stirbar was added solid $LiAlH_4$ (7.34 g, 193 mmol) and dry THF (286 mL) under a nitrogen atmosphere. The mixture was cooled in an ice bath (0 °C) and **2.6** (28.6 g, 164 mmol) dissolved in THF (107.25 mL) was added dropwise via camula. After addition, the reaction was warmed to rt (23 °C) and allowed to react for 6 h. The mixture was then cooled in an ice bath (0 °C) and quenched with 15% NaOH in H_2O (100 mL). The resulting mixture was then extracted with ethyl acetate (9 x 20 mL). The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude oil was purified by column chromatography (silica 20:1 petroleum ether:ethyl acetate) to yield **2.7** as a colorless oil (14 g, 80 mmol, 96%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (m, 6H), 1.50 (m, 3H), 1.57 (m, 1H),

4.00 (dd, 1H, *J* = 2.5 Hz, 6.5 Hz), 4.33 (m, 1H), 4.54 (d, 1H, *J* = 4.0 Hz), 5.89 (d, 1H, *J* = 3.75 Hz); HRMS [M+Na] calc= 197.0784, obs= 197.0788; R_f = 0.68 (3:1 petroleum ether:ethyl acetate) *The experimental data for this compound matched those previously reported in the literature.

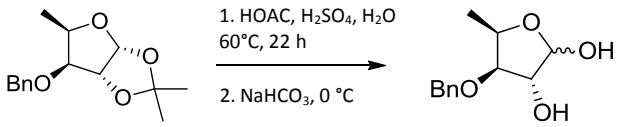
Synthesis of **2.3**:



2.7 2.3

Synthesis of (3aR,5R,6S,6aR)-6-(benzyloxy)-2,2,5-trimethyltetrahydrofuro[2,3-d][1,3]dioxole (**2.3**). To a flame dried 2.0 L RBF equipped with a magnetic stirbar was added solid sodium hydride (25 g, 1.0 mol, 60%) and THF (150 mL) were combined and stirred for 20 min under a nitrogen environment in an ice bath (0 °C). A solution of benzyl bromide (8.7 mL, 13 g, 73 mmol), **2.7** (9.9 g, 57 mmol), and THF (300 mL) was added slowly over 50 min. After addition, the mixture was warmed to rt (23 °C) and allowed to stir for 20 h. The reaction was cooled in an ice bath (0 °C) and carefully quenched with methanol. This mixture was extracted with diethyl ether (4x 30 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting oil was purified by column chromatography (silica, 6:1 petroleum ether:ethyl acetate) to yield **2.3** as a yellow oil (13.5 g, 52.3 mmol, 92%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (d, 6H, *J* = 5.25 Hz), 1.48 (s, 3H), 3.72 (d, 1H, *J* = 3.0 Hz), 4.33 (m, 1H), 4.49 (dd, 1H, *J* = 12.25 Hz, 61 Hz), 4.54 (d, 1H, *J* = 4 Hz), 5.91 (d, 1H), 7.35 (m, 5H); HRMS [M+Na] calc= 287.1254, obs= 287.1249; R_f = 0.96 (2:1 petroleum ether:ethyl acetate)

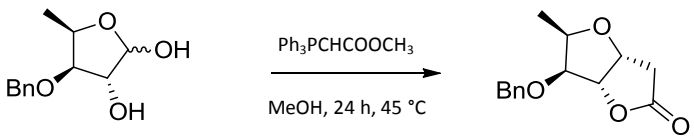
Synthesis of **2.10**:



2.3 2.10

Synthesis of (3R,4R,5R)-4-(benzyloxy)-5-methyltetrahydrofuran-2,3-diol (**2.10**). To a 500 mL RBF equipped with a magnetic stirbar was added **2.3** (13.5 g, 60.2 mmol), glacial acetic acid (216 mL), H_2O (54 mL), and H_2SO_4 (6.75 mL). This solution was heated in an oil bath (60 °C) for 22 h. The mixture was cooled in an ice bath (0 °C) and powered $NaHCO_3$ (55 g) was added until the resulting mixture was neutral. The solution was evaporated under reduced pressure and the resulting mixture was purified by column chromatography (silica, 3:1 petroleum ether:ethyl acetate) to yield **2.10** as a yellowish oil (6.2 g, 28 mmol, 54% mixture of diastereomers). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (d, 3H, *J* = 6.5 Hz), 1.39 (d, 3H, J = 6.5 Hz), 3.81 (m, 1H), 4.24 (m, 1H), 4.45 (m, 1H), 4.59 (m, 1H), 4.74 (m, 1H), 5.09 (s, 1H), 5.49 (d, 1H, *J* = 4.25 Hz), 7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.31, 26.20, 26.68, 38.16, 65.69, 71.61, 82.78, 82.83, 97.35, 104.78, 111.21, 127.49, 127.59, 127.98, 128.41, 128.50, 128.79, 137.62, 137.75, 160.78 HRMS [M+Na] calc= 247.0941, obs= 247.0937; R_f = 0.40 (5:1 petroleum ether:ethyl acetate)

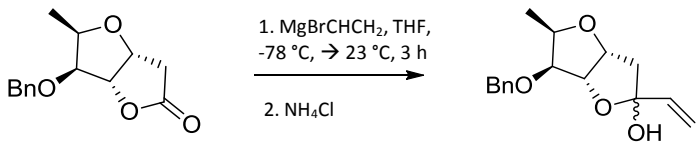
Synthesis of **2.14**:



2.10 2.14

Synthesis of (3aR,5R,6S,6aS)-6-(benzyloxy)-5-methyltetrahydrofuro[3,2-b]furan-2(5H)-one (**2.14**). To a 1 L mL RBF equipped with a magnetic stirbar was added **2.10** (3.83 g, 17.1 mmol), methanol (370 mL), and methyl (triphenylphosphoranylidene)acetate (11.44 g, 34.22 mmol). This solution was heated in an oil bath (45 °C) for 24 h. The reaction was then concentrated under reduced pressure and purified by column chromatography (silica, 7:1 petroleum ether:ethyl acetate) to yield **2.14** as a colorless oil (4.5 g, 13 mmol, 78%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (d, 3H, *J* = 6.3 Hz), 2.64 (m, 2H), 3.96 (d, 1H, *J* = 3.5 Hz), 4.16 (m, 1H), 4.65 (m, 2H), 4.89 (dd, 2H, *J* = 12.5 Hz, 31.25 Hz), 7.35 (m, 5H), ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.64, 35.92, 65.27, 72.47, 81.99, 85.79, 128.14, 137.23, 140.9, 175.4; LRMS= 248.1; R_f= 0.40 (2:1 petroleum ether:ethyl acetate) (6:1 petroleum ether:ethyl acetate**)**

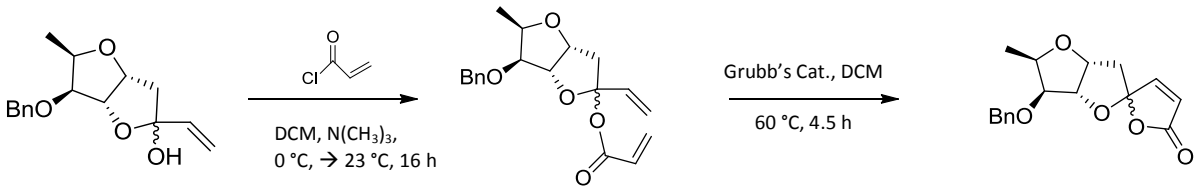
Synthesis of **2.9**:



2.14 2.9

Synthesis of (2R,3aR,5R,6S,6aS)-6-(benzyloxy)-5-methyl-2-vinylhexahydrofuro[3,2-b]furan-2-ol (**2.9**). To a flame dried 100 mL RBF was equipped with a magnetic stirbar was added vinyl magnesium bromide (0.26 mL, 0.25 g, 0.26 mmol) and THF (4 mL) under a nitrogen environment. The solution was cooled in a acetone/dry ice bath (-78 °C) and stirred for 20 min. A solution of **2.14** (0.0422 g, 0.1701 mmol) in THF (3 mL) was added slowly while the reaction was kept at -78 °C. The reaction was warmed to rt (23 °C) and allowed to proceed for 3 h. The reaction was then quenched with NH_4Cl (5 mL) and then concentrated under reduced pressure. Purification by column chromatography (silica, 5:1 petroleum ether:ethyl acetate) yield **2.9** as a colorless oil (0.03 g, 0.11 mmol, 64%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 (d, 3H, *J* = 7.5 Hz), 1.62 (s, 1H), 1.97 (d, 1H, *J* = 7.5 Hz), 2.17 (s, 2H), 2.91 (s, 1H), 3.74 (d, 1H, *J* = 5 Hz), 4.30 (m, 2H), 4.64 (dd, 1H, *J* = 12.5 Hz, 45 Hz), 5.16 (m, 1H), 5.26 (q, 1H, *J* = 10 Hz), 5.90 (m, 1H) 7.33 (m, 5H); R_f= 0.27 (6:1 petroleum ether:ethyl acetate)

Synthesis of **2.16/2.17**:



2.9 2.16 2.17

Synthesis of (2S,3aR,5R,6S,6aS)-6-(benzyloxy)-5-methyl-2-vinylhexahydrofuro[3,2-b]furan-2-yl acrylate (**2.16**). To a flame dried 100 mL RBF was equipped with a magnetic stirbar was added **2.9** (0.08 g, 0.29 mmol), DCM (3 mL), and triethyl amine (0.8 mL) under a nitrogen environment. The solution was cooled in an ice bath (0 °C) and acryloyl chloride (0.05 mL, 0.06 g, 0.62 mmol)

was added slowly. The reaction was stirred at rt (23 °C) for 16 h. The solution was evaporated under reduced pressure, filtered, and purified by column chromatography (silica, 3:1 petroleum ether:ethyl acetate) to yield **2.16** as a colorless oil (0.07 g, 0.21 mmol, 73%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.24 (d, 3H, *J* = 5 Hz), 1.58 (s, 2H), 3.75 (m, 1H), 4.32 (m, 2H), 4.56 (m, 1H), 4.73 (dd, 1H, *J* = 10 Hz, 67.5 Hz), 5.33 (m, 3H), 6.00 (m, 2H), 6.43 (m, 1H), 7.04 (m, 1H) 7.33 (m, 3H) 7.37 (m, 1H), 7.55 (m, 1H); R_f= 0.70 (6:1 petroleum ether:ethyl acetate)

Synthesis of **2.17**:

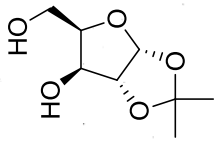
Synthesis of (2R,3a'R,5'R,6'S,6a'S)-6'-(benzyloxy)-5'-methyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-4(5H)-one (**2.17**). To a flame dried 50 mL RBF was equipped with a magnetic stirbar was added **2.16** (0.04 g, 0.11 mmol), DCM (2 mL), and Grubbs cat. (0.03 g, 0.04 mmol) in a nitrogen environment. The reaction was sealed and headed in an oil bath (60 °C) for 4.5 hours. The mixture was filtered (silica plug) to yield a 2:3 mixture of **2.16** and **2.17**. R_f= 0.67 (6:1 petroleum ether:ethyl acetate)

Studies toward the Total Synthesis of (+)-Pyrenolide D

Appendix 1: ^{1}H and ^{13}C NMR Spectra

JD-54 2 1 U:\data\rsweeney\nmr

ARBON_OSU CDCl3 {C:\Bruker\TopSpin3.0} rsweeney 54



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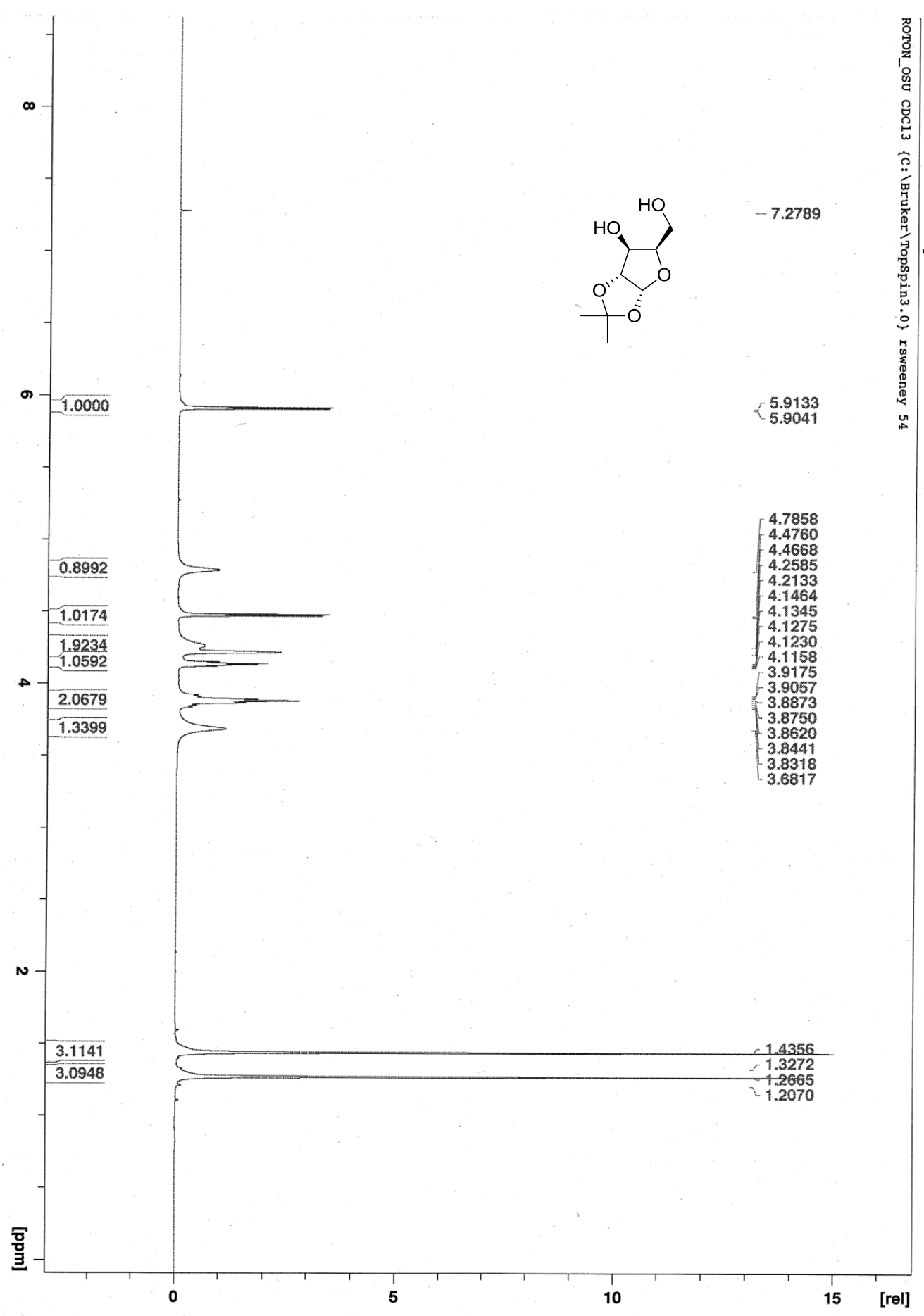
JD-54 1 1 U:\data\rsweeney\nmr
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O
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4.2133
4.1464
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4.1230
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3.8873
3.8750
3.8620
3.8441
3.8318
3.6817
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1.3272
1.2665
1.2070
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1.9234
1.0592
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1.3399
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3.0948
8
6
4
2
[ppm]
0
5
10
15
[rel]

JD-51 2 1 U:\data\rsweeney\nmr

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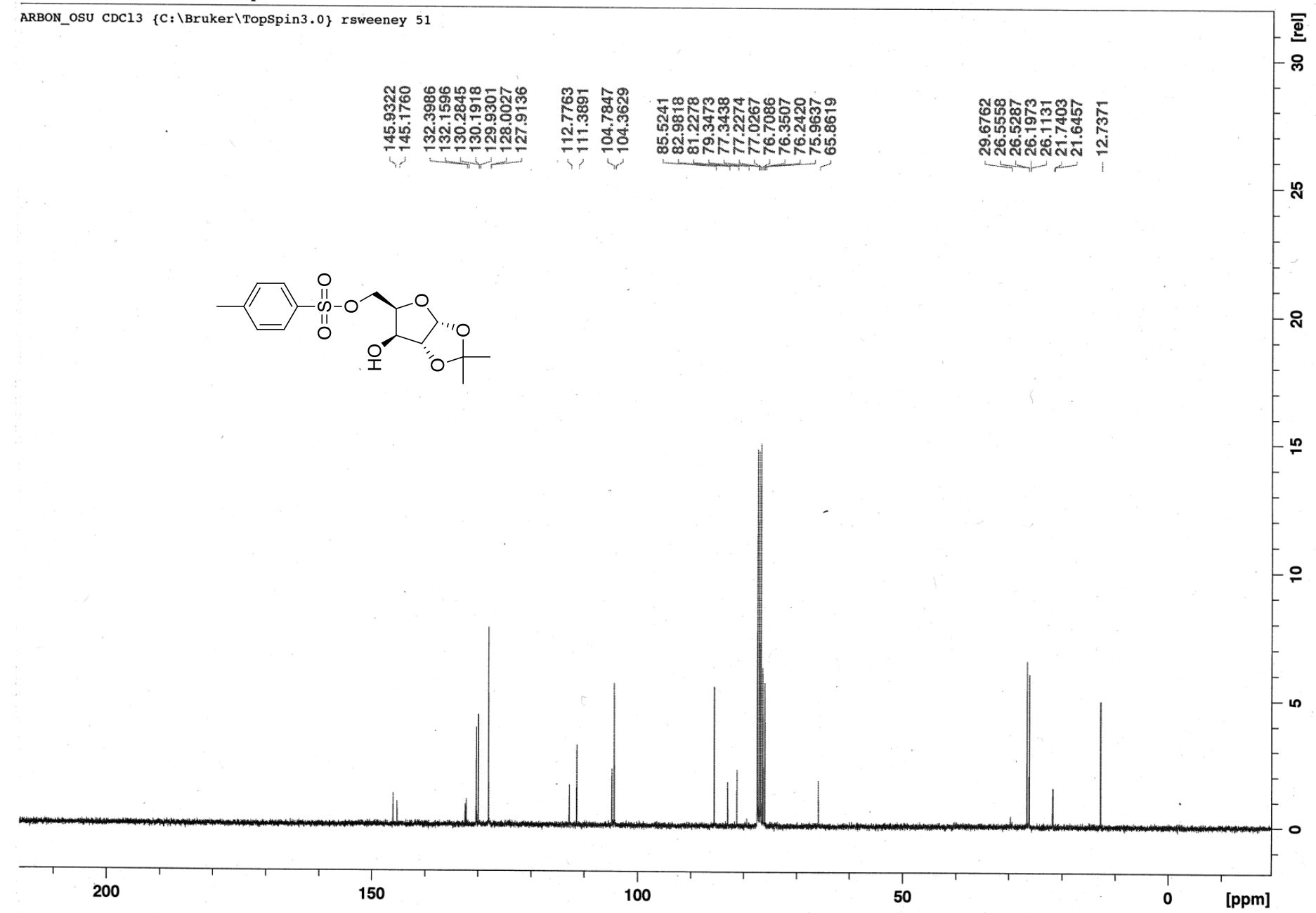

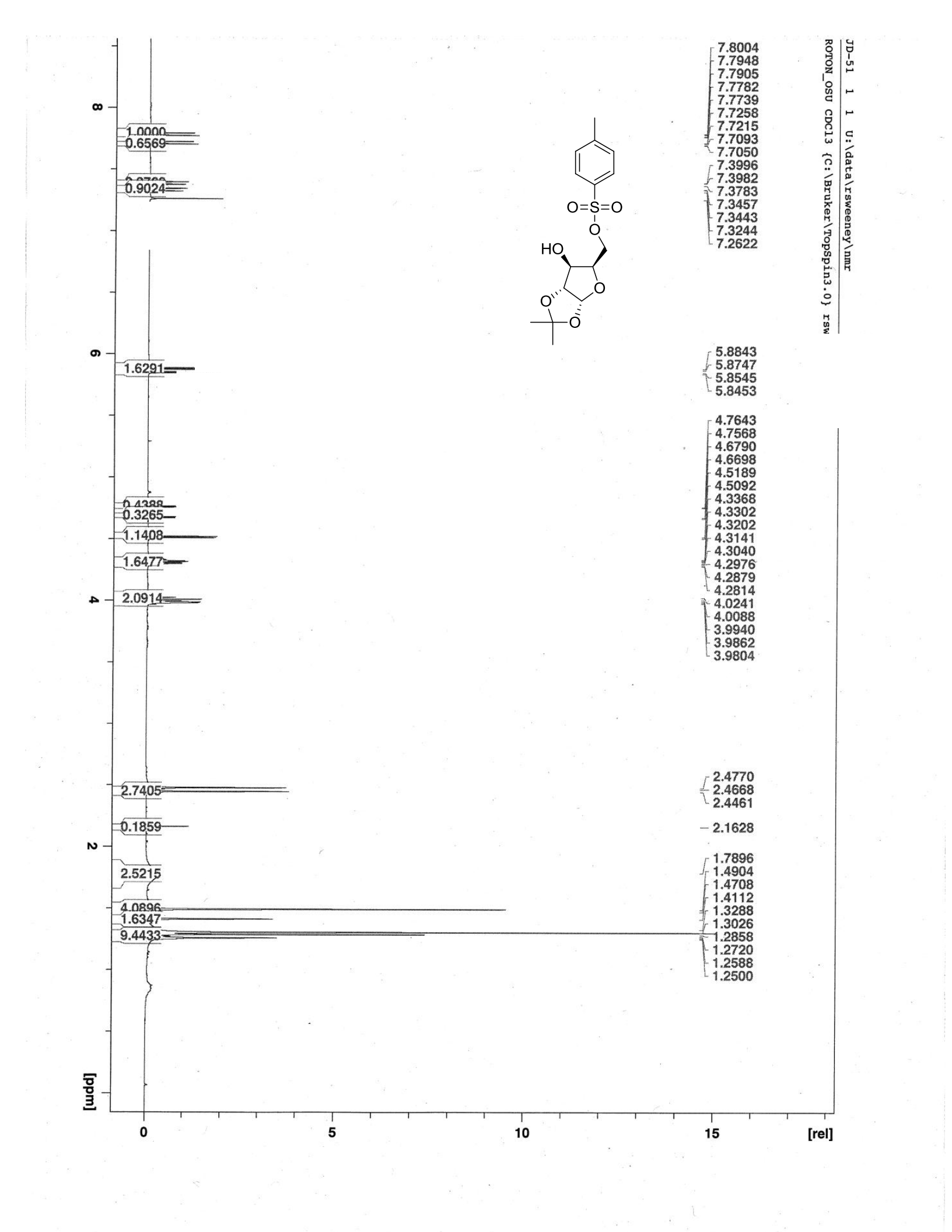
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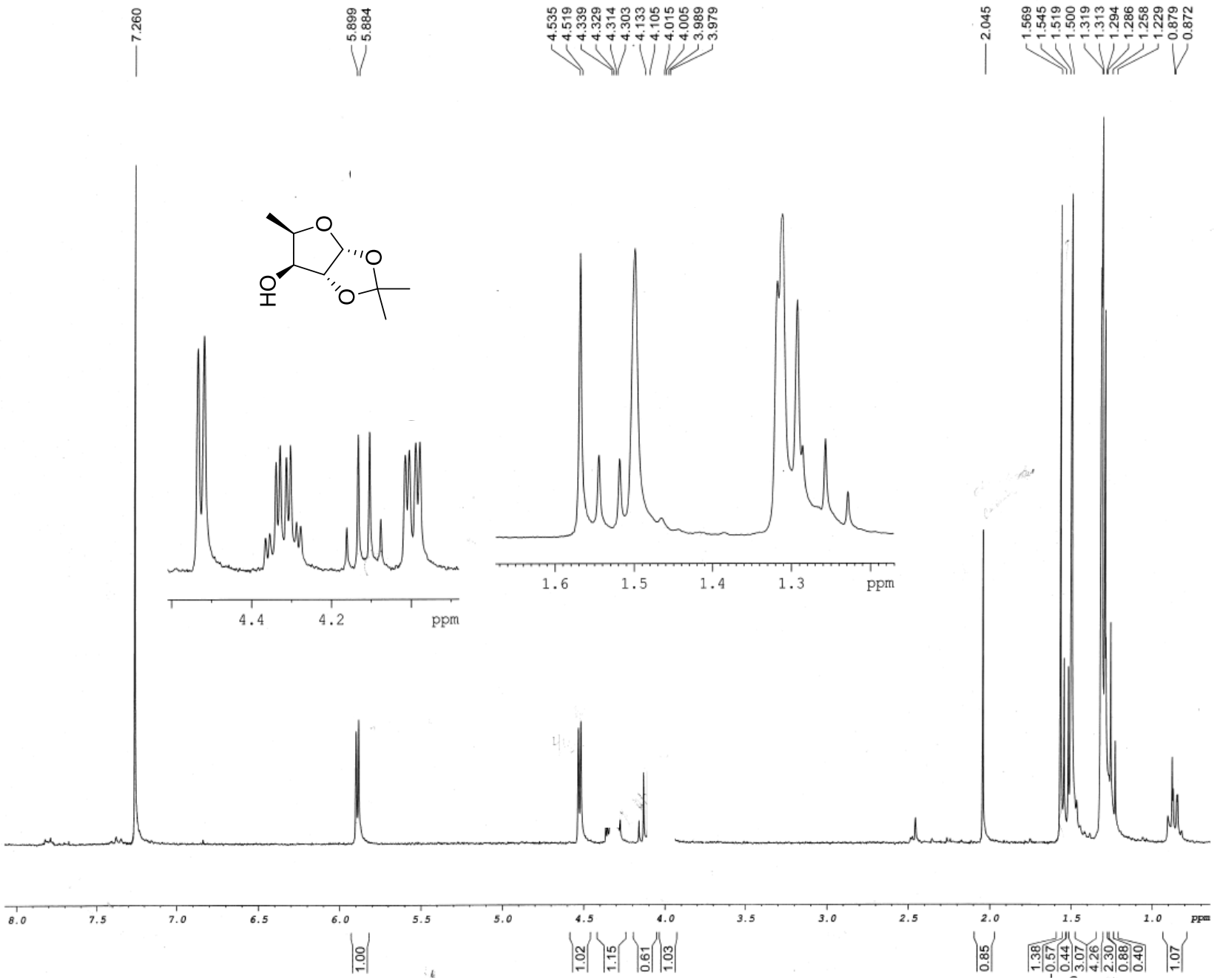

THE OHIO STATE UNIVERSITY
CHEMISTRY [illegible]NT
NMR F

Current Data Params
NAME Journal Reduced Compound 7-13-2009
EXPNO 1
PROCNO 1

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F2 - Processing parameters

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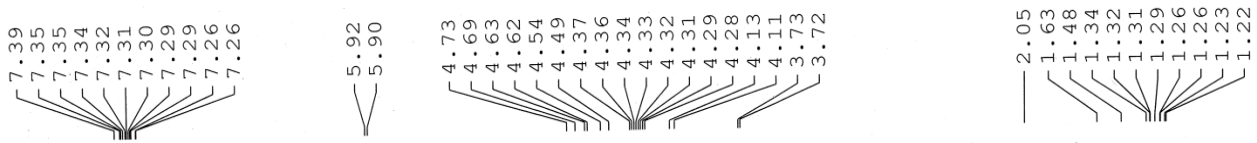
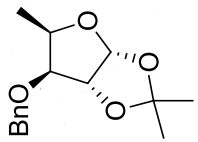


The Ohio State University
Department of Chemistry
NMR Facility



Current Data Parameters

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EXPNO	2
PROCNO	1

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SFO1	250.1315447 MHz

F2 - Processing parameters

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JD-50 2 1 U:\data\rsweeney\nmr

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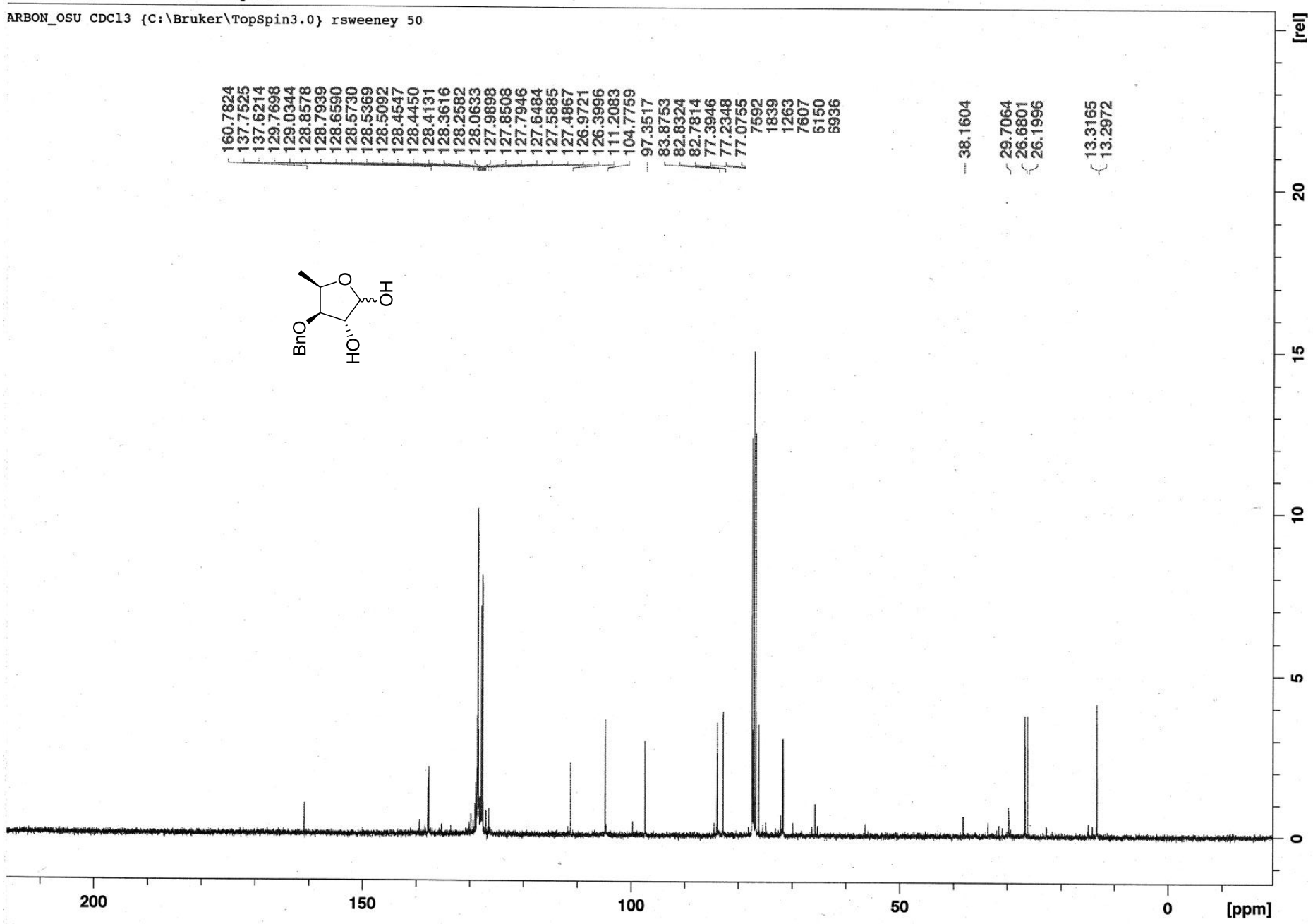

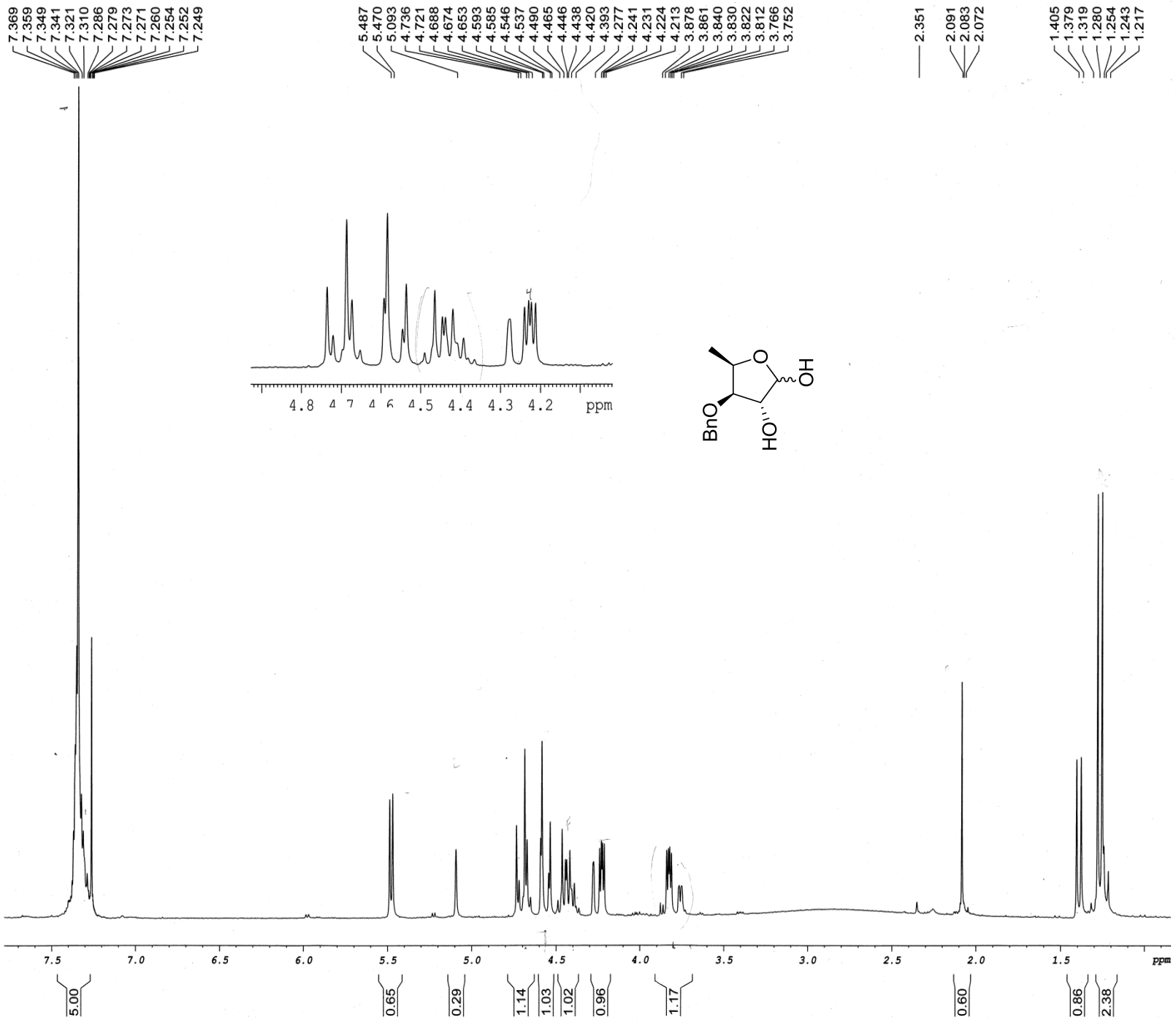

THE OHIO STATE UNIVERSITY
CHEMISTRY DEPARTMENT
NMR FACILITY

Current Data Parameters

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EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

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F2 - Processing parameters

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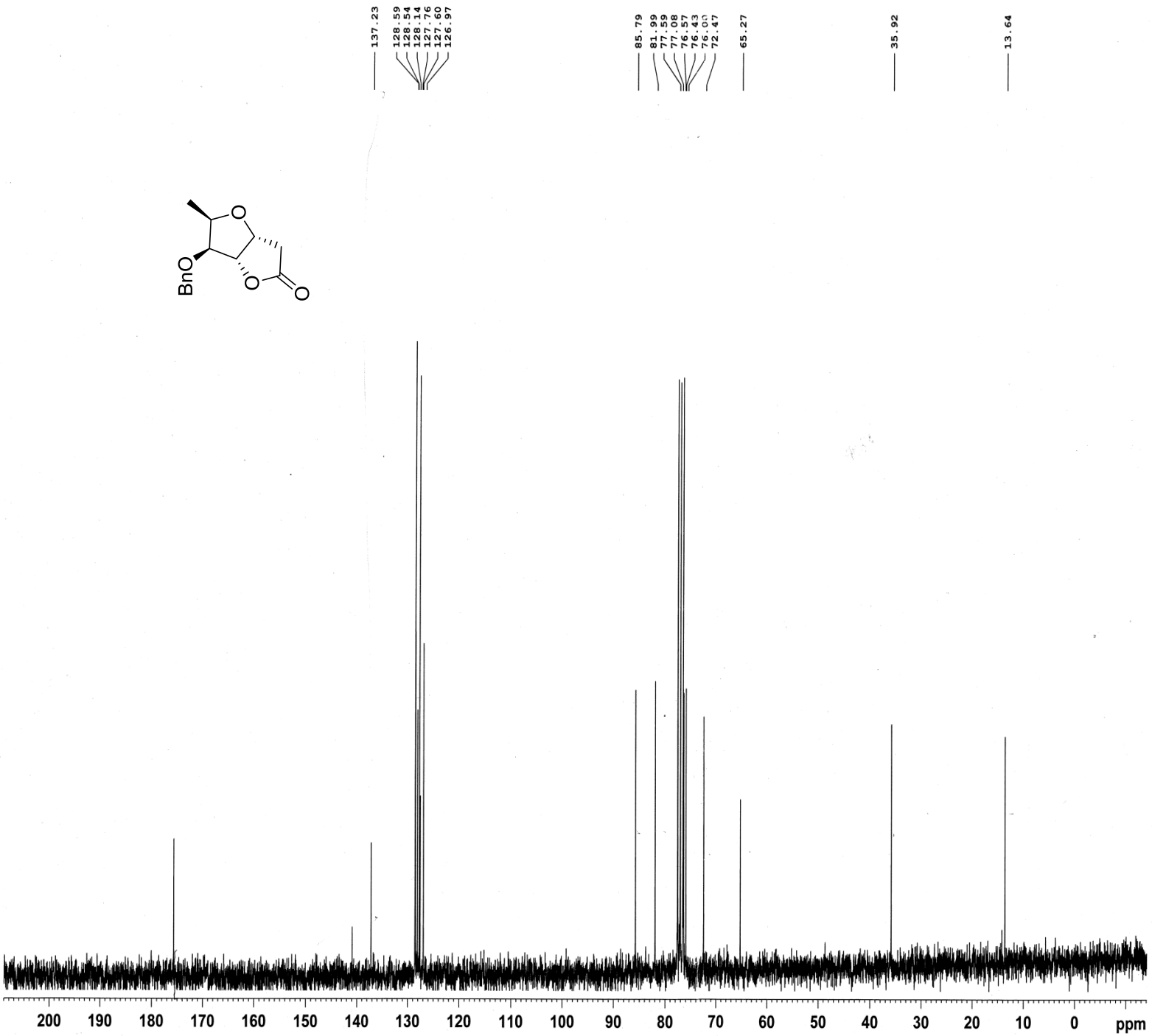

BRUKER

Current Data Parameters
NAME adam lactone carbon
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters

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NUC1	13C
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PL1	0.00 dB
SFO1	62.9015280 MHz

======== CHANNEL f2 ========

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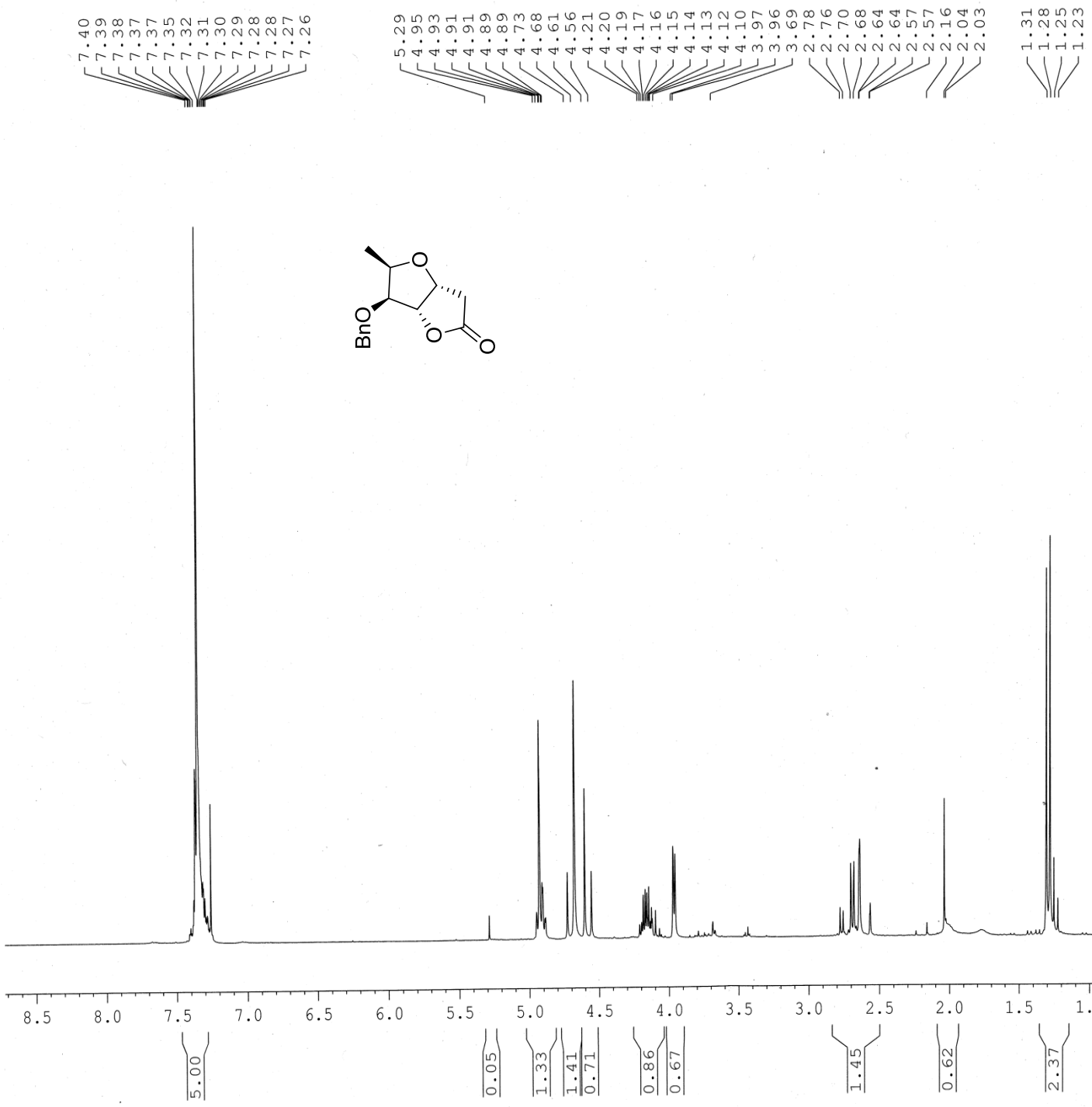
PL2	-4.00 dB
PL12	16.00 dB
PL13	120.00 dB
SFO2	250.1310005 MHz

F2 - Processing parameters

SI	32768
SF	62.8952390 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00



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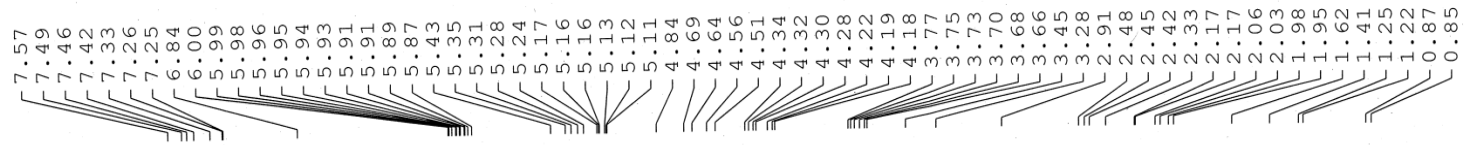
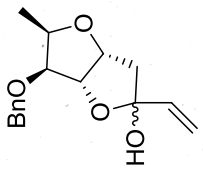
```
Current Data Par
NAME        adam
EXPNO              2
PROCNO             1

F2 - Acquisition Paramet
Date_       20100827
Time           14.18
INSTRUM        spect
PROBHD   5 mm QNP 1H/13
PULPROG         zg30
TD             41406
SOLVENT        CDCl3
NS                16
DS                 2
SWH          5175.983 Hz
FIDRES       0.125006 Hz
AQ           3.9998696 sec
RG             143.7
DW              96.600 usec
DE               6.00 usec
TE              291.2 K
D1           1.00000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1               1H
P1               7.20 usec
PL1             -4.00 dB
SFO1       250.1315447 MHz

F2 - Processing parameters
SI             32768
SF         250.1300002 MHz
WDW               EM
SSB                0
LB              0.30 Hz
GB                 0
PC              1.00
```





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Current Data Parameters

NAME	pure alcohol last
EXPNO	1
PROCNO	1

F2 - Acquisition Parameter

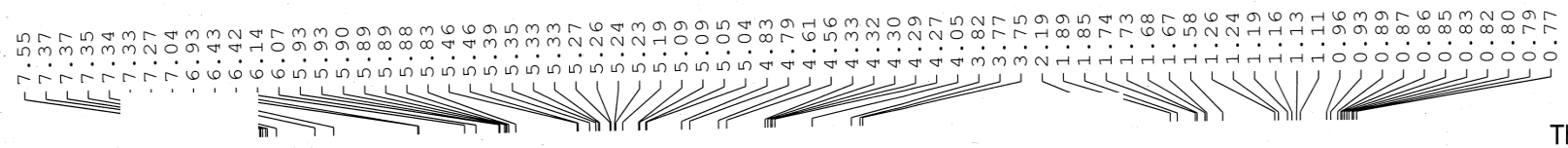
Date_	20111206
Time	10.21
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	41406
SOLVENT	CDCl3
NS	16
DS	2
SWH	5175.983 Hz
FIDRES	0.125006 Hz
AQ	3.9998696 sec
RG	645.1
DW	96.600 usec
DE	6.00 usec
TE	294.2 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	7.20 usec
PL1	-4.00 dB
SFO1	250.1315447 MHz

F2 - Processing parameters

SI	32768
SF	250.1300005 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



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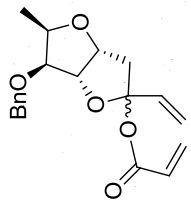


```
Current Data Parameters
NAME      ester stock 1
EXPNO                1
PROCNO               1

F2 - Acquisition Parameter
Date_         20111214
Time             17.32
INSTRUM          spect
PROBHD   5 mm QNP 1H/13
PULPROG          zg30
TD               41406
SO   NT          CDCl3
NS                  16
DS                   2
SW            5175.983 Hz
FI   S        0.125006 Hz
AQ            3.9998696 sec
RG                1024
DW               96.600 usec
DE                6.00 usec
TE               294.2 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                 1H
P1                7.20 usec
PL1              -4.00 dB
SFO1       250.1315447 MHz

     Processing parameters
                 32768
          250.1299971 MHz
                   EM
                    0
LB               0.30 Hz
GB                  0
PC                1.00
```